

**CENTER FOR DRUG EVALUATION AND  
RESEARCH**

**APPLICATION NUMBER: 21-141 and 21-176**

**STATISTICAL REVIEW(S)**

## Statistical Review and Evaluation

NDA#: 21-141

APR 27 2000

Applicant: Geltex Pharmaceuticals, Inc.

Name of Drug: Welchol (colesevelam hydrochloride)

Documents Reviewed: Vols 1.20, 1.23, 1.24, 1.25

Medical Officer: Shiao Shen, M.D., HFD-510

### Background

In all, the sponsor has submitted 7 randomized, double-blind, placebo-controlled, multi-center trials in support of Welchol's (W) efficacy in lowering LDL-C as monotherapy and in combination with HMG-CoA reductase inhibitors. There are 5 trials subject to review: 2 monotherapy- GTC-48-301, GTC-48-302, and 3 combination- GTC-37-203 (W/lovastatin), GTC-48-204 (W/simvastatin), and GTC-48-205 (W/atorvastatin). The combination studies compared dosages and regimens of the combination to each single component and to placebo. The Medical Division has stipulated that the additional LDL-C lowering due to W should be an absolute 6% over that of the statin. The primary endpoint is in terms of percent change from baseline. The durations of treatment for each trial were as follows: 301-6 months, 302-6 weeks, 203-4 weeks, 204-6 weeks, and 205-4 weeks. Sample sizes were not computed for specific powers but were determined based upon ICH considerations. Protocols either do not specify an analysis plan or it states that when the normal distribution assumption is not satisfied, a non-parametric test will be used. In fact, treatment comparisons were done using t-tests or Wilcoxon rank sum tests depending on the inspection of normality.

### Results

Results did not depend upon dropouts. The dropout rates for each trial were 301:20%, 302:8%, 203:12%, 204:7%, and 205:5%.

**Table 1** displays the demographic summary for the five trials under review. *Note that the trials testing the combinations (203, 204, 205) enrolled patients with much higher levels of LDL-C than patients in the monotherapy studies (301, 302).*

**Table 2** displays the summary results for the monotherapy treatment groups in all five trials. All active groups were statistically significantly better than placebo even using a Bonferroni adjustment for multiple comparisons within each trial (\*s refer to within group comparisons to baseline). **In all five trials, at least 3.8 g monotherapy of W/day was needed to achieve an approximate average of 15% change from baseline.** In the highest dose group in each monotherapy study, the 25<sup>th</sup> %ile, 50<sup>th</sup> %ile, and 75<sup>th</sup> %ile of percent reduction in LDL-C were approximately 9%, 18% and 25%, respectively. There was no average difference in the reduction of LDL-C between patients with <160 mg/dL

LDL-C and those with > 160 mg/dL LDL-C at baseline.

**Table 3** displays the full results in the three combination studies while **Table 4** displays the p-values for the pair-wise comparisons among treatment arms. **Table 3** indicates that the minimum additional lowering due to any W combination over and above that of the respective statin is 8%. **Table 4** indicates that all comparisons between the combinations and the respective statin were nominally statistically significant. Moreover, all p-values from the relevant tests are small enough so that they are still significant at the .05 level.

#### Summary

The statistical aspects of this application are straightforward. Results of these studies demonstrate Welchol's statistically significant differences from placebo and statistically significant contributions of Welchol to the combination of Welchol and either simvastatin, atorvastatin or lovastatin. The treatment differences, as represented by point estimates of the average of individuals' changes from baseline LDL-C are sufficient according to HFD-510. In addition, there was no evidence that results depended upon age (above or below 65), race or gender.

*/s/*  
David Hoberman, Ph.D.  
Mathematical Statistician

Concur: Dr. Sahlroot:

*/s/* 4/18/00

Dr. Nevius:

*/s/* 4/27/00

Arch NDA#: 21-141

HFD-510

HFD-510/SShen, DOrloff, BKoch

HFD-715/DHoberman, TSahlroot, ENevius, Chron

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TABLE 1

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	GTC-37-201	GTC-37-202	GTC-48-301	GTC-48-302	GTC-37-203	GTC-48-204	GTC-48-205
Mean age (Range in years)	56 (31 to 80)	55.4 (21 to 83)	55.5 (18 to 86)	53.9 (24 to 70)	57.7 (23 to 88)	54.8 (21 to 84)	57.2 (28 to 79)
Gender: n (%)							
Male	65 (44)	69 (57)	232 (49.7)	46 (48.9)	59 (45)	133 (53)	54 (59.3)
Female	82 (56)	53 (43)	235 (50.3)	48 (51.1)	72 (55)	118 (47)	37 (40.7)
Race:							
Caucasian	121 (82)	113 (93)	419 (89.7)	94 (100)	112 (85.5)	237 (94.4)	76 (83.5)
Black	18 (12)	6 (5)	34 (7.3)	0 (0)	13 (9.9)	8 (3.2)	8 (8.8)
Hispanic	3 (2)	2 (2)	6 (1.3)	0 (0)	2 (1.5)	1 (0.4)	3 (3.3)
Asian	5 (3)	1 (1)	4 (0.9)	0 (0)	4 (3.1)	4 (1.6)	2 (2.2)
Baseline LDL							
< 160	ND	ND	267 (57.2)	37 (39.4)	ND	33 (13.1)	7 (7.7)
160 to 190			172 (36.8)	40 (42.6)	104 (79.4)	132 (52.6)	55 (60.4)
> 190			27 (5.8)	17 (18.1)	27 (20.6)	86 (34.3)	29 (31.9)
Previous MI	ND	ND	8 (2)	1 (1)	ND	13 (5)	1 (1)
CAD	ND	ND	13 (3)	1 (1)	ND	21 (8)	2 (2)
Diabetes mellitus	ND	ND	14 (3)	1 (1)	ND	2 (1)	0
HTN	ND	ND	92 (20)	21 (22)	ND	56 (22)	12 (13)
Family history of premature CHD	ND	ND	98 (21)	14 (15)	ND	71 (28)	15 (17)
Current cigarettes	ND	ND	31 (7)	12 (13)	ND	32 (13)	6 (7)

TABLE 2

DOSE	N	BASELINE (MG/DL)		ENDPOINT (MG/DL)		CHANGE (MG/DL)		PERCENT CHANGE	
		MEAN	MEDIAN	MEAN	MEDIAN	MEAN	MEDIAN	MEAN	MEDIAN
GTC-48-301									
Placebo	88	155	152	155	155	0	1	0	1
Cholestagel 2.3 g	99	161	160	146	146	-14****	-16****	-9****	-9****
Cholestagel 3.0 g	90	160	156	141	139	-19****	-21****	-12****	-12****
Cholestagel 3.8 g	95	159	154	135	134	-24****	-24****	-15****	-16****
Cholestagel 4.5 g	94	156	157	127	125	-28****	-29****	-18****	-20****
GTC-48-302									
Placebo	22	169	167	174	169	4	4	3	3
CG 3.8 g AM	25	168	163	137	137	-31****	-30****	-18****	-19****
CG 3.8 g PM	23	165	162	141	143	-24****	-24****	-15****	-14****
CG 1.9 g b.i.d.	24	174	163	142	138	-32****	-29****	-18****	-15****
GTC-37-203									
Placebo	26	171	176	172	176	1	2	0	1
Cholestagel 2.3 g	29	172	170	158	156	-13**	-14**	-7**	-8**
GTC-48-204									
Placebo	33	184	182	177	177	-7*	-7*	-4**	-4**
Cholestagel 2.3 g	36	186	183	169	166	-17****	-18****	-8****	-9****
Cholestagel 3.8 g	37	198	187	167	155	-31****	-30****	-16****	-16****
GTC-48-205									
Placebo	19	185	178	191	180	6	-2	3	-1
Cholestagel 3.8 g	16	184	182	163	160	-22**	-24**	-12**	-12**

\*p < 0.05, \*\*p < 0.01, \*\*\*p < 0.001, \*\*\*\*p < 0.0001

p values based on t-test (normality met) and Wilcoxon Signed-Rank test (normality not met)

TABLE 3

DOSE	N	BASELINE (MG/DL)		ENDPOINT (MG/DL)		CHANGE (MG/DL)		PERCENT CHANGE	
		MEAN	MEDIAN	MEAN	MEDIAN	MEAN	MEDIAN	MEAN	MEDIAN
GTC-37-203 Lovastatin									
Placebo	26	171	176	172	176	1	2	0	1
Cholestagel 2.3 g	29	172	170	158	156	-13**	-14**	-7**	-8**
Lovastatin 10mg	26	168	169	129	130	-39****	-42****	-22****	-26****
CG 2.3 g/lov 10mg dosed together	27	174	173	115	117	-60****	-57****	-34****	-33****
CG 2.3 g/lov 10mg dosed apart	23	169	167	116	114	-53****	-48****	-32****	-31****
GTC-48-204 Simvastatin									
Placebo	33	184	182	177	177	-7*	-6*	-4**	-4**
Cholestagel 2.3 g	36	186	183	169	166	-17****	-18****	-8****	-9****
Cholestagel 3.8 g	37	198	187	167	155	-31****	-30****	-16****	-16****
Simvastatin 10 mg	35	183	172	136	127	-48****	-52****	-26****	-30****
Simvastatin 20 mg	39	180	176	119	118	-61****	-60****	-34****	-33****
CG 2.3 g/sim 20mg	37	191	184	111	103	-80****	-80****	-42****	-42****
CG 3.8 g/sim 10mg	34	196	179	116	104	-80****	-83****	-42****	-42****
GTC-48-205 Atorvastatin									
Placebo	19	185	178	191	180	6	-2	3	-1
Cholestagel 3.8 g	16	184	182	163	160	-22**	-24**	-12**	-12**
Atorvastatin 10 mg	18	182	172	114	113	-68****	-67****	-38****	-38****
CG 3.8 g/ato 10mg	18	187	183	98	99	-89****	-84****	-48****	-49****
Atorvastatin 80 mg	20	182	179	86	82	-96****	-101****	-53****	-56****

\*p < 0.05, \*\*p < 0.01, \*\*\*p < 0.001, \*\*\*\*p < 0.0001

p values based on t-test (normality met) and Wilcoxon Signed-Rank test (normality not met).

TABLE 4

**Paired Comparisons Between Treatment Groups for Percent Change in LDL Cholesterol: Simvastatin**

PARAMETER (MG/DL)/ TREATMENT	CG 2.3 G	CG 3.8 G	SIM 10 MG	SIM 20 MG	CG 2.3 G/ SIM 20 MG	CG 3.8 G/ SIM 10 MG
Placebo	0.0377	< 0.0001	< 0.0001	< 0.0001	< 0.0001	< 0.0001
CG 2.3 g		0.0135	< 0.0001	< 0.0001	< 0.0001	< 0.0001
CG 3.8 g			0.0013	< 0.0001	< 0.0001	< 0.0001
SIM 10 mg				0.0546	< 0.0001	< 0.0001
SIM 20 mg					0.0010	0.0052
CG 2.3g/ SIM 10 mg						0.6744

Values based on contrasts of ANOVA (normality met) and Wilcoxon Sign-Rank test (normality not met).

PARAMETER (MG/DL)/ TREATMENT	CG 3.8 G	ATO 10 MG	CG 3.8 G/ATO 10 MG	ATO 80 MG
Placebo	0.0007	< 0.0001	< 0.0001	< 0.0001
CG 3.8 g		< 0.0001	< 0.0001	< 0.0001
ATO 10 mg			0.0072	0.0002
CG 3.8 g/ ATO 10 mg				0.0699

Values based on contrasts of ANOVA (normality met) and Wilcoxon Sign-Rank test (normality not met).

PARAMETER (MG/DL) /TREATMENT	CG 2.3 G	LOVA 10 MG	CG 2.3 G/ LOVA 10 MG DOSED TOGETHER	CG 2.3 G/ LOVA 10 MG DOSED APART
Placebo	0.0146	< 0.0001	< 0.0001	< 0.0001
CG 2.3 g		< 0.0001	< 0.0001	< 0.0001
Lova 10 mg			0.0002	0.0042
CG 2.3 g/Lova 10 mg dosed together				0.4803

Values based on contrasts of ANOVA with factor treatment to compare mean changes between paired treatment groups.

**STATISTICAL REVIEW AND EVALUATION  
CARCINOGENICITY**

Date: **MAR 17 2000**  
NDA No: 21-141  
Applicant: Geltex Pharmaceuticals, Inc.  
Drug Name: CholestaGel®  
Data Source: two diskettes - mice and rats  
Pharmacologist: Gemma Kuijpers, ODE2, HFD-510  
Statistical Reviewer: Moh-Jee Ng, Div II/OEB, HFD-715

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## 1. Introduction

This reviewer evaluated the mouse and rat carcinogenicity studies of CholestaGel® for its carcinogenic potential. The studies were conducted by \_\_\_\_\_ In this report, this reviewer presents to the reviewing pharmacologist, Dr. Kuijpers, the results of her independent carcinogenicity analysis based on the sponsor's data.

## 2. Designs of the Studies

Information about the study designs is summarized in the following table.

Species	Mouse	Rat
Strain	Swiss, Crl: CD®-1 (ICR) BR	— Sprague-Dawley — SD strain
Route of Administration	oral	oral
Dose Unit	Mg/kg/day	Mg/kg/day
Dose Level (Control 1, Control 2, Low, Medium, High)	0, 0, 0.3, 1.0, 3.0	0, 0, 0.4, 1.2, 2.4
Number of Animals/per treatment group	50 (main study) 15 (satellites)	60 (main study) 10 (satellites)
Length of Study	104 weeks	104 weeks

In each of these experiments there were two control groups and three treated groups received CholestaGel®. The animals in the control group 1 received basal diet and those in control group 2 received vitamin supplemented diet. The treated groups (3, 4 and 5) received doses of 0.3, 1.0 and 3.0 mg/kg/day for mice and 0.4, 1.2 and 2.4 mg/kg/day for rats. The terminal sacrifice started on and after weeks 104.

## 3. Sponsor's Findings

The sponsor statistical analysis of the mortality and tumor data of the main studies was based on the Proc Chronic Program. There was no histopathological evaluation on mice and rats in Satellite groups.

The sponsor statistical analysis used data of Groups 1, 2 and 5 only in the rats study. Tumor data of Groups 3 and 4 were not included since microscopic examinations were not performed on all tissues/organs in those groups.

The sponsor concluded that there was an increase in tumor incidence in C-cell adenomas in thyroid gland in male rats but not in female rats.

Finally, the sponsor concluded that dietary administration of CholestaGel® to Sprague-Dawley rats and albino mice for up to 2-year did not produce any toxic or tumorigenic effect that could be related to treatment.

#### 4. Reviewer's Evaluation

This reviewer performed independent analyses on the survival and tumor data submitted by the sponsor, using the programs developed by Dr. Ted Guo of Division of Biostatistics II. The primary statistical methods used were described in Peto *et al* (1980), and Lin and Ali (1994). These methods adjust differences in animal mortality and take contexts of observation of the tumors into consideration. The intervals used for the adjustment of mortality were 0-52, 53-78, 79-91, and 92-104 weeks and terminal sacrifice for animals.

The statistical analyses of carcinogenicity study data consists of two parts, namely, the survival data analysis and the tumor data analysis. The survival data analysis is: 1) to examine the differences in survival distributions among the treatment groups (homogeneity test); and 2) to determine if there is a positive linear trend in the proportion of deaths with respect to the dose levels (Linear trend test). Two statistical tests were used in the survival data analysis: the Cox test and the generalized Kruskal-Wallis test. The theoretical background of these tests was described in Lin and Ali (1994) and Thomas *et al* (1977).

The tumor data analysis is: 1) to determine if there is a positive linear trend in the proportions of a selected tumor type in a selected organ/tissue with respect to the dose levels. The tumors were classified as either fatal (lethal) or non-fatal (non-lethal), according to Peto *et al* (1980). The reviewer applied the death-rate method to fatal tumors and the prevalence method to non-fatal tumors. For tumors that caused death for some, but not for all, animals, a combined test was performed.

A rule for adjusting the effect of multiple tests proposed by Haseman (1983) can be used in control-high pairwise comparisons. Haseman's rule says that rare tumors should be tested at 0.05 level of significance and common tumors should be tested at 0.01 level of significance. A similar rule proposed by the Divisions of Biometrics, CDER/FDA for trend tests was used in this review for tests for positive trend. The rule states that in order to keep the overall false-positive rate at the nominal level of approximately 0.1, rare tumor types should be tested at 0.025 significance level, otherwise (common tumors) at 0.005 significance level (Lin and Rahman, 1988). A tumor type with spontaneous rate of 1% or less is defined as rare, and as common, otherwise.

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## 4.1 Evaluation of Carcinogenicity Study on Male Mice

This reviewer's evaluation comprises the following components:

- Survival data analysis
- Tumor data analysis

### 4.1.1 Survival Data Analysis

The survival data analysis determines whether the dose-mortality trend is statistically significant. A positive result indicates that more deaths are likely to occur as the dose level increases. Table 1a below includes, for the male mice, the number of deaths, the numbers at risk, and the cumulate percentages of deaths by treatment and age group. The time interval "105-106" represents the terminal-sacrifice interval.

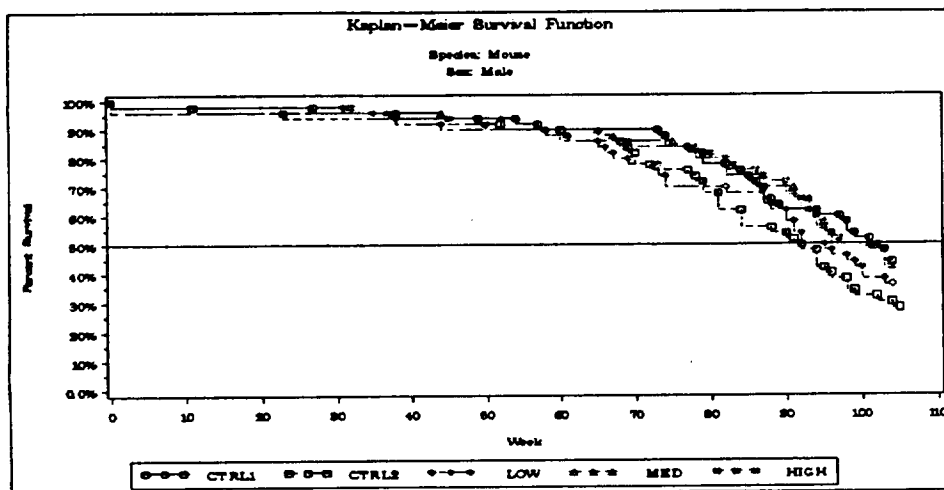
**Table 1a**  
**Cumulative Percentages of Deaths in Male Mice**

Analysis of Mortality Species: Mouse Sex: Male															
Week	CTRL1			CTRL2			Dose LOW			MED			HIGH		
	NUM. of Dead	NUM. at Risk	CUMU Pct. Died	NUM. of Dead	NUM. at Risk	CUMU Pct. Died	NUM. of Dead	NUM. at Risk	CUMU Pct. Died	NUM. of Dead	NUM. at Risk	CUMU Pct. Died	NUM. of Dead	NUM. at Risk	CUMU Pct. Died
0-52	2	50	4.0	4	50	8.0	4	50	8.0	3	50	6.0	4	50	8.0
53-78	6	48	16.0	9	46	26.0	9	46	26.0	5	47	16.0	4	46	16.0
79-91	10	42	36.0	11	37	48.0	8	37	42.0	7	42	30.0	8	42	32.0
92-104	10	32	56.0	11	26	70.0	11	29	64.0	11	35	52.0	13	34	58.0
105- 106	22	50	44.0	15	50	30.0	18	50	36.0	24	50	48.0	21	50	42.0

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Figure 1 presents plot of Kaplan-Meier estimates of the survival distribution of the treatment groups of male mice.

**Figure 1: Kaplan-Meier Survival Functions for Male Mice**



The test for dose-mortality trend (Table 2a) shows no significant results based on the Cox test and the Kruskal-Wallis test. The tests also show no statistically significant dose-mortality trend in male mice.

**Table 2a: Dose-Mortality Trend in Male Mice**

Dose-Mortality Trend Tests			
This test is run using Trend and Homogeneity Analyses of Proportions and Life Table Data Version 2.1, by Donald B. Thomas, National Cancer Institute			
Species: Mouse			
Sex: Male			
Method	Time-Adjusted Trend Test	Statistic	P Value
Cox	Dose-Mortality Trend	0.82	0.3666
	Depart from Trend	4.55	0.2073
	Homogeneity	5.37	0.2510
Kruskal-Wallis	Dose-Mortality Trend	0.39	0.3201
	Depart from Trend	4.59	0.2048
	Homogeneity	5.57	0.2333

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#### 4.1.2 Tumor Data Analysis

The tumor data analysis determines whether the dose-tumor positive linear trend in tumor incidence is statistically significant. This reviewer tested this trend for every organ and tumor with data provided by the sponsor. This reviewer analyzed

the dose-tumor trend among the two control groups and treated group 2, 3, and 4. The resulting p-values are compared against the p-value cutoff points set by the FDA procedures. A significant result indicates a dose-tumor positive linear trend.

This reviewer's analysis does not find any statistically significant dose-tumor positive linear trend in the male mice.

#### **4.1.3 Conclusions on Male Mice Study**

This reviewer's survival data analysis and tumor data analysis were consistent with the sponsor's analysis results of the male mice study. There was no significant difference in survival between treatment groups and no significant positive trends in tumor incidence in the tumor types tested in male mice.

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## 4.2 Evaluation of Carcinogenicity Study on Female Mice

This reviewer's evaluation comprises the following components:

- Survival data analysis
- Tumor data analysis

### 4.2.1. Survival Data Analysis

The survival data analysis determines whether the dose-mortality trend is statistically significant. A positive result indicates that the higher the dose level is, the more deaths are likely to occur. The Table 1b below includes, for the female mice, the number of deaths, the numbers at risk, and the cumulate percentages of deaths by treatment and age group. The time interval "105-106" represents the terminal-sacrifice interval.

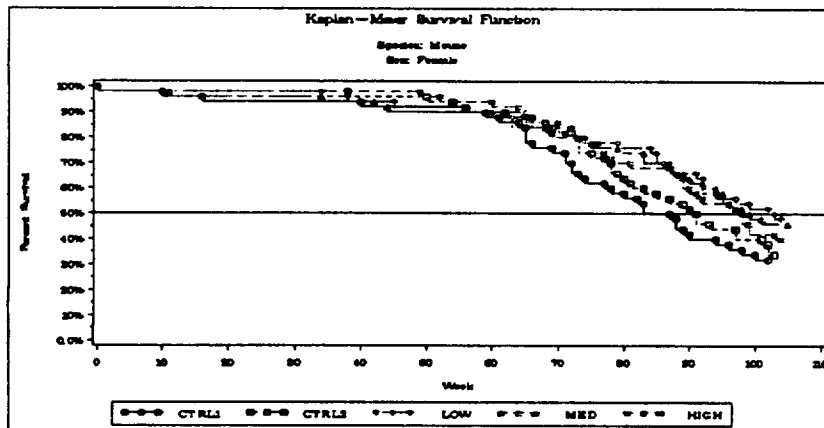
**Table 1b**  
**Cumulative Percentages of Deaths in Female Mice**

Analysis of Mortality																
Species: Mouse																
Sex: Female																
Week	Dose															
	CTRL1			CTRL2			LOW			MED			HIGH			
	Num. of Dead	Num. at Risk	Cumu Pct. Died	Num. of Dead	Num. at Risk	Cumu Pct. Died	Num. of Dead	Num. at Risk	Cumu Pct. Died	Num. of Dead	Num. at Risk	Cumu Pct. Died	Num. of Dead	Num. at Risk	Cumu Pct. Died	
0-52	3	50	6.0	2	50	4.0	3	50	6.0	4	50	8.0	2	50	4.0	
53-78	17	47	40.0	13	48	30.0	7	47	20.0	7	46	22.0	12	48	28.0	
79-91	9	30	58.0	10	35	50.0	7	40	34.0	7	39	36.0	7	36	42.0	
92-104	5	21	68.0	8	25	66.0	9	33	52.0	8	32	52.0	9	29	60.0	
105-106	16	50	32.0	17	50	34.0	24	50	48.0	24	50	48.0	20	50	40.0	

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Figure 2 presents plot of Kaplan-Meier estimates of the survival distribution of the treatment groups of female mice

**Figure 2: Kaplan-Meier survival functions for female mice**



The test for dose-mortality trend (Table 2b) shows no significant results based on the Cox test and the Kruskal-Wallis test.

**Table 2b: Dose-Mortality Trend in Female Mice**

Dose-Mortality Trend Tests			
This test is run using Trend and Homogeneity Analyses of Proportions and Life Table Data Version 2.1, by Donald G. Thomas, National Cancer Institute			
Species: Mouse Sex: Female			
Method	Time-Adjusted Trend Test	Statistic	P Value
Cox	Dose-Mortality Trend	0.59	0.4412
	Depart from Trend	5.60	0.1339
	Homogeneity	6.19	0.1854
Kruskal-Wallis	Dose-Mortality Trend	0.91	0.3467
	Depart from Trend	5.82	0.1299
	Homogeneity	6.73	0.1511

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#### 4.2.2 Tumor Data Analysis

The tumor data analysis determines whether the dose-tumor positive linear trend in tumor incidence is statistically significant. This reviewer tested this trend for every organ and tumor with data provided by the sponsor. This reviewer analyzed the dose-tumor trend among the two control groups and treated group 2, 3, and 4. The resulting p-values are compared against the p-value cutoff points set by the FDA procedures. A significant result indicates a dose-tumor positive linear trend.



This reviewer's analysis does not find any statistically significant dose-tumor positive linear trend in tumor incidence in the tumor types tested in the male mice.

#### **4.2.3 Conclusions on Female Mice**

This reviewer's survival data analysis and tumor data analysis were consistent with the sponsor's analysis results based on the female mice study. There was no significant difference in survival between treatment groups and no significant positive trends in tumor incidence in male mice.

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#### 4.2.4 Evaluation of Validity of the Design

This reviewer's analysis did not find any tumor with a significant positive trend. However, before drawing the conclusion that the drug is not carcinogenic in mice, it is important to look into the following two issues as pointed out in the paper by Haseman (1984). The two issues are:

- 1) Were enough animals exposed for a sustained amount of time to the risk of late developing tumors ?
- 2) Were dose levels high enough to pose a reasonable tumor challenge to the animals ?

This is no consensus among experts regarding as number of animals and length of time at risk, although most carcinogenicity studies are designed to run for two years with fifty animals per treatment group. The following are some rules of thumb regarding these two issues suggested by experts in this field: Haseman (1984) investigated on the first issue. He gathered data from 21 studies using Fisher 344 rats and B6C3F1 mice conducted at the National Toxicology program (NTP). It was found that, on an average, approximately 50% of the animals in the high dose group survived the two-year study period. Haseman suggested that, as a rule of thumb, a 50% survival of 50 initial animals in the high dose group, between weeks 80-90, would consider as a sufficient number of animals under an adequate exposure. However, the percentage can be lower or higher if the number of animals used in each treatment/sex group is larger or smaller than 50 so that there will be between 20-30 animals still alive during these weeks. In addition, Chu, Cueto, and Ward (1981), suggested that "To be considered adequate, an experiment that has not shown a chemical to be carcinogenic should have groups of animals with greater than 50% survival at one-year." It appears, from the sources, that the proportions of survival at 52 weeks, 80-90 weeks, and two years are of interest in determining the adequacy of exposure and number of animals at risk."

For the adequacy of the chosen dose levels, it is generally accepted that the high dose should be close to the MTD (maximum tolerated dose). Chu, Cueto, and Ward (1981) suggested:

- I) "A dose is considered adequate if there is a detectable loss in weight gain of up to 10% in a dosed group relative to the controls."
- II) "The administered dose is also considered an MTD if dosed animals exhibit clinical signs or severe histopathologic toxic effects attributed to the chemical."
- III) "In addition, doses are considered adequate if the dosed animals show a slight increased mortality compared to the controls."

Bart, Chu, and Tarone (1979) stated that the mean body weight curves over the entire study period should be taken into consideration with the survival curves, when adequacy of dose levels is to be examined. In particular, "usually, the comparison should be limited to the early weeks of a study when no or little mortality has yet occurred in any of the groups. Here a depression of the mean

weight in the treated groups is an indication that the treatment has been tested on levels at or approaching the MTD."

Based on the above suggestion and recommendations, this reviewer examines the validity of the experimental design of the mice study.

The table below summarizes the survival data of mice in the high dose group.

	End of 52 weeks	End of study weeks (104)
Male	96%	40%
Female	98%	46%

From the percentages in the table above and the survival criteria mentioned, it may be reasonable to conclude that there were enough mice exposed for a sustained amount of time to the drug.

There were detectable losses in weight gain increment were in the dosed groups as compared the control groups. The table below summarizes the percentage of weight gain increment as compare to the control groups for mice.

#### Body Weight Gains for Mice

	Treatment Groups	Mean Body Weight (grams)		Mean Body Weight Gain (gram)	% Difference in MBWG Control 1	% Difference in MBWG Control 2
		Beginning Study	End of Study			
Male	Control 1	28.87	38.60	33.74		
	Control 2	28.81	38.85	33.83		
	Low	28.54	40.07	34.31	2	2
	Medium	28.69	38.07	33.38	-1	-1
	High	28.63	37.06	32.85	-3	-3
Female	Control 1	22.71	37.38	30.05		
	Control 2	22.49	34.51	28.5		
	Low	22.42	35.88	29.15	-3	2
	Medium	22.66	34.86	28.76	-4	1
	High	22.63	33.19	27.91	-7	-2

From the results of the table above, one can see that the percentages of weight gain for dosed male mice and female mice are less than 10%. These suggest that the high dose levels for males and females were close to the MTD. To draw a conclusion in this regard, all clinical signs and histopathologic effects in the treated rats should be taken into considered.

### 4.3 Evaluation of Carcinogenicity Study on Male Rats

This reviewer's evaluation comprises the following components:

- Survival data analysis
- Tumor data analysis

#### 4.3.1 Survival Data Analysis

The survival data analysis determines whether the dose-mortality trend is statistically significant. A positive result indicates that the higher the dose level is, the more deaths are likely to occur. The Table 1c below includes, for the male rats, the number of deaths, the numbers at risk, and the cumulate percentages of deaths by treatment and age group. The time interval "105-106" represents the terminal-sacrifice interval.

**Table 1c**  
**Cumulative Percentages of Deaths in Male Rats**

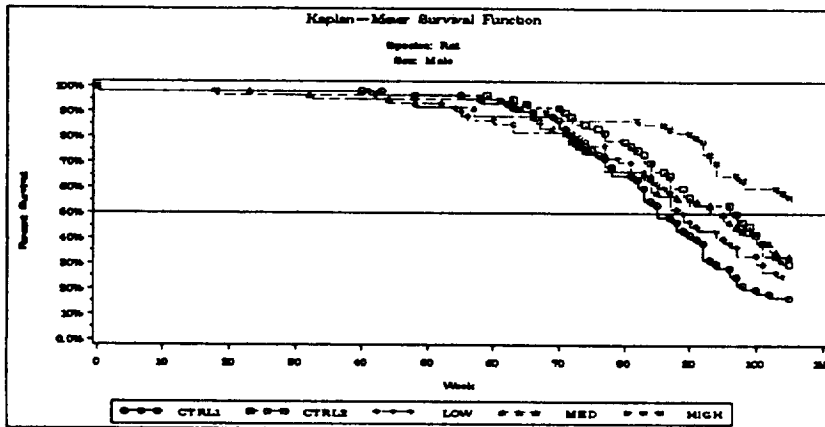
Analysis of Mortality  
Species: Rat  
Sex: Male

Week	Dose														
	CTRL1			CTRL2			LOW			MED			HIGH		
	Num. of Dead	Num. at Risk	Cumu Pct. Died	Num. of Dead	Num. at Risk	Cumu Pct. Died	Num. of Dead	Num. at Risk	Cumu Pct. Died	Num. of Dead	Num. at Risk	Cumu Pct. Died	Num. of Dead	Num. at Risk	Cumu Pct. Died
0-52	1	60	1.7	1	60	1.7	4	60	6.7	4	60	6.7	2	60	3.3
53-78	18	59	31.7	10	59	18.3	10	56	23.3	12	56	26.7	5	58	11.7
79-91	17	41	60.0	15	49	43.3	19	46	55.0	11	44	45.0	5	53	20.0
92-104	13	24	81.7	15	34	68.3	12	27	75.0	12	33	65.0	13	48	41.7
105-106	11	60	18.3	19	60	31.7	15	60	25.0	21	60	35.0	35	60	58.3

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Figure 3 presents plot of Kaplan-Meier estimates of the survival distribution of the treatment groups of male rats

**Figure 3: Kaplan-Meier Survival Functions for Male Rats**



The test for dose-mortality trend shows significant results in the Cox test ( $p < 0.0001$ ) and the kruskal-Wallis test ( $p < 0.0001$ ). Results of the dose-mortality trend test are presented in Table 2c below.

**Table 2c: Dose-Mortality Trend in Male Rats**

Dose-Mortality Trend Tests			
This test is run using Trend and Homogeneity Analysis of Proportions and Life Table Data Version 2.1, by Donald G. Thomas, National Cancer Institute			
Species: Rat			
Sex: Male			
Method	Time-Adjusted Trend Test	Statistic	P Value
Cox	Dose-Mortality Trend	18.65	0.0000
	Depart from Trend	7.03	0.0708
	Homogeneity	25.68	0.0000
Kruskal-Wallis	Dose-Mortality Trend	15.35	0.0001
	Depart from Trend	7.51	0.0572
	Homogeneity	22.88	0.0001

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This reviewer's survival data analysis concluded that the positive increase in mortality in male rats is dose-related. Therefore, the age-adjusted trend test detailed in the following section (Tumor Data Analysis) is justified.

#### 4.3.2 Tumor Data Analysis

The tumor data analysis determines whether the dose-tumor positive linear trend in tumor incidence is statistically significant. This reviewer tested this trend for every organ and tumor with data provided by the sponsor. This reviewer analyzed the dose-tumor trend of the two control groups and treated group 2, 3, and 4. The resulting p-values are compared against the p-value cutoff points set by the FDA procedures.

The sponsor claimed that the tumor data analysis was conducted only on Groups 1, 2 and 5 due to the fact that microscopic examinations were not performed on all tissues and organs of animals in Groups 3 and 4. This reviewer included groups 3 and 4 in her tumor data analysis because the number of histopathology findings of these groups was not less than 45% of the total.

This reviewer performed dose-tumor trend tests among the two control groups and treated groups 2, 3, and 4 (Table 5c) as well as pairwise tests between the two control groups and the treated group 5 (Table 5e).

The incidence rates and p-values of tumor types showing significant trends or differences are summarized in the following Table 3c.

**Table 3c: Significant Trend Test for Male Rats**

Organ	Tumor	Tumor-Bearing Animal	P-value
Pancreas (51)	Acinar cell adenoma (5106)	0, 0, 0, 2, 3	=0.002 *

\* indicate statistically significant at level 0.025

A statistically positive dose-response relationships ( $p=0.025$ ) in incidence rate of acinar cell adenoma in pancreas was detected.

#### 4.4.2 Conclusion on Male-Rat Study

In the 2-year male rat study, there was a statistically significant positive linear trend in mortality. There was a statistically positive-dose relationship in acinar cell adenoma in pancreas.

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#### 4.4 Evaluation of Carcinogenicity Study on Female Rats

This reviewer's evaluation comprises the following components:

- Survival data analysis
- Tumor data analysis

##### 4.4.1 Survival Data Analysis

The survival data analysis determines whether the dose-mortality trend is statistically significant. A positive result indicates that the higher the dose level is, the more deaths are likely to occur. The Table 4a below includes, for the female rats, the number of deaths, the numbers at risk, and the cumulate percentages of deaths by treatment and age group. The time interval "105-106" represents the terminal-sacrifice interval.

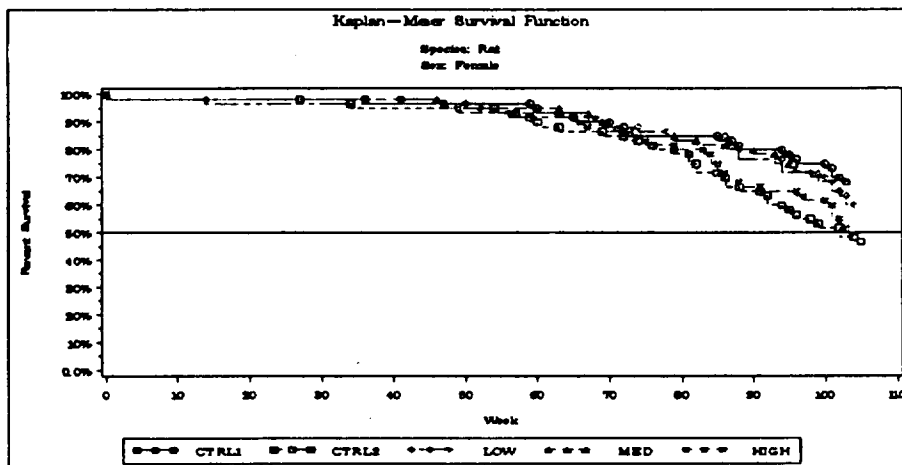
**Table 4a**  
**Cumulative Percentages of Deaths in Female Rats**

Analysis of Mortality																
Species: Mouse																
Sex: Female																
Week	CTRL1			CTRL2			Dose			MED			HIGH			
							LOW									
	NUM. of Dead	NUM. at Risk	Cumu Pct. Died	NUM. of Dead	NUM. at Risk	Cumu Pct. Died	NUM. of Dead	NUM. at Risk	Cumu Pct. Died	NUM. of Dead	NUM. at Risk	Cumu Pct. Died	NUM. of Dead	NUM. at Risk	Cumu Pct. Died	
0-52	3	50	6.0	2	50	4.0	3	50	6.0	4	50	8.0	2	50	4.0	
53-78	17	47	40.0	13	48	30.0	7	47	20.0	7	46	22.0	12	48	28.0	
79-91	9	30	58.0	10	35	50.0	7	40	34.0	7	39	36.0	7	36	42.0	
92-104	5	21	68.0	8	25	66.0	9	33	52.0	8	32	52.0	9	29	60.0	
105-106	16	50	32.0	17	50	34.0	24	50	48.0	24	50	48.0	20	50	40.0	

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Figure 4 presents plot of kaplan-Meier estimates of the survival distributions of the treatment groups for female rats.

**Figure 4: Kaplan-Meier survival functions for female rats**



The test for dose-mortality trend shows no significant results based on the Cox test and the kruskal-Wallis test .

**Table 4c: Dose-Mortality Trend in Female Rats**

Dose-Mortality Trend Tests			
This test is run using Trend and Homogeneity Analyses of Proportions and Life Table Data Version 2.1, by Donald G. Thomas, National Cancer Institute			
Species: Rat			
Sex: Female			
Method	Time-Adjusted Trend Test	Statistic	P Value
Cox	Dose-Mortality Trend	0.34	0.5614
	Depart from Trend	0.57	0.0356
	Homogeneity	0.81	0.0634
Kruskal-Wallis	Dose-Mortality Trend	0.32	0.5714
	Depart from Trend	0.37	0.0380
	Homogeneity	0.69	0.0693

Source: c:\ng\XAnlmlX.txt

This reviewer's survival data analysis concluded that there was no statistical significance in survival distribution among the treatment groups.



#### **4.4.2 Tumor Data Analysis**

The tumor data analysis determines whether the dose-tumor positive linear trend in tumor incidence is statistically significant. This reviewer tested this trend for every organ and tumor with data provided by the sponsor. This reviewer analyzed the dose-tumor trend of the two control groups and treated group 2, 3, and 4. The resulting p-values are compared against the p-value cutoff points set by the FDA procedures.

The sponsor claimed that the tumor data analysis was conducted only on Groups 1, 2 and 5 due to the fact that microscopic examinations were not performed on all tissues and organs of animals in Groups 3 and 4. This reviewer included groups 3 and 4 in her tumor data analysis because the number of histopathology findings of these groups was not less than 45% of the total.

This reviewer performed dose-tumor trend tests among the two control groups and treated groups 2, 3, and 4 (Table 5d) as well as pairwise comparisons between the two control groups and treated group 5 (Table 5f).

There was no significant positive linear trend in incidence rates in tumor data in female rats.

#### **4.4.3 Conclusion on Female Rat Study**

This reviewer's survival data analysis and tumor data analysis were consistent with the sponsor's results of the female rats study. In the 2-year female rat study there was no significant difference in survival between treatment groups and no significant positive trends in tumor incidence in the tumor types tested.

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**Signoff Page**

Statistical Reviewer: Moh-Jee Ng

Signature: /S/ Date: 3/17/00

Concur: Karl K. Lin, Ph.D.  
Expert Mathematical Statistician  
(Applications in Pharmacology & Toxicology)

Signature: /S/ Date: 3/17/00

cc: Original NDA 21-141  
HFD-510/Division File  
HFD-510/Gkuijpers  
HFD-510/MSimoneau  
HFD-715/Division File  
HFD-715/KLin  
HFD-715/MNg  
HFD-715/Tssahlroot  
HFD-715/ENevius

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## Appendix

### Statistical Interpretation of Significance in Evaluation of Tumor -Data Analyses Currently Adopted by CDER Office of Biostatistics

#### Test of Dose-Tumor Positive Linear Trend

- \* Exact Test - The statistical interpretation of significance is based on the exact test, if one of the two following situation applies.

1. The tumor is found either fatal to all the animals or non-fatal to all the animals.
2. The tumor is fatal only to some but not to all animals, and time-intervals for both situations of lethality do not overlap.

The exact test is done using the Permutation test with general scores, which are the actual dose values. When the scores are set to be equally spaced, the above test is known as the Cochran-Armitage test.

- \* Asymptotic test - The statistical interpretation of significance is based on the asymptotic test, if none of the above situations applies. The asymptotic test uses the Z-statistic, following the standard normal distribution.

- \* Cutoff Point for P-Value - To adjust for the effect of multiple testing, one can use a rule proposed by Haseman. A modified rule, proposed by the Divisions of Biometrics, CDER/FDA is applied to the trend tests in the review. In order to keep the overall type-I error at the level of about 10%, this rule states:

1. Tumors with a spontaneous tumor rate of 1% or less may be tested at the 0.025 significance level.
2. Otherwise, the 0.005 significance level may be used.

#### Test using pairwise comparisons

1. Tumors with a spontaneous tumor rate of 1% or less may be tested at the 0.05 significance level.
2. Otherwise, the 0.01 significance level may be used.

**Table 5a**  
**Analysis of Carcinogenic Potential in Male Mouse**  
**Test of Dose-Response (Tumor) Positive Linear Trend**  
Study No. A1B2C37X8YZ9

Run Date & Time: March 13, 2000 (14:21)

Source: c:\ng\XAnimalX.txt

Note: Dose Levels Included: CTRL1 CTRL2 LOW MED HIGH (0 0 0.3 1 3)  
Missing value in Tumor-Caused Death is treated as tumor not causing death  
Tumor Type: IN: Incidental (nonfatal) tumor, FA: Fatal tumor.

ORGAN/TISSUE NAME AND TUMOR NAME	(ORG#) (TMR#)	TUMOR TIME TYPES STRATA	ROW NO.	2x2 CONTINGENCY -----TABLES-----	EXACT ASYMP ASYMP PROB PROB PROB /CONT CORR =P(STAT .GE. OBSERVED)
ADRENAL	(1	) IN 92-104	1	1 0 0 0 0	0.680 0.697 0.795
CORTICALADENOMA	(108	) IN 92-104	2	9 11 11 11 12	
		IN 105-106	1	0 0 0 1 0	
		IN 105-106	2	22 15 18 23 21	
Spontaneous tumor pct: <= 1% in ctrl. - Total				1 0 0 1 0	
BRAIN	(10	) FA 86	1	1 0 0 0 0	1.000 0.788 0.891
GLIOMA	(1003	) FA 86	2	36 31 35 40 39	
Spontaneous tumor pct: <= 1% in ctrl. - Total				1 0 0 0 0	
FAT	(26	) IN 105-106	1	0 0 0 0 1	0.210 0.033 0.082
HEMANGIOMA	(2602	) IN 105-106	2	22 15 18 24 20	
Spontaneous tumor pct: <= 1% in ctrl. - Total				0 0 0 0 1	
HARDERIANGLAND	(28	) IN 79-91	1	0 0 0 1 0	0.433 0.436 0.482
ADENOMA	(2803	) IN 79-91	2	10 11 8 6 8	
		IN 92-104	1	0 3 0 0 3	
		IN 92-104	2	10 8 11 11 10	
		IN 105-106	1	2 2 2 1 1	
		IN 105-106	2	20 13 15 23 20	
Spontaneous tumor pct: 7% in ctrl. - Total				2 5 2 2 4	
HARDERIANGLAND	(28	) IN 92-104	1	1 0 0 0 0	1.000 0.789 0.890
ADENOCARCINOMA	(2810	) IN 92-104	2	9 11 11 11 13	
Spontaneous tumor pct: <= 1% in ctrl. - Total				1 0 0 0 0	
JEJUNUM	(35	) IN 105-106	1	1 0 0 0 0	1.000 0.791 0.894
LEIOMYOMA	(3509	) IN 105-106	2	21 15 18 24 21	
Spontaneous tumor pct: <= 1% in ctrl. - Total				1 0 0 0 0	
JEJUNUM	(35	) IN 105-106	1	0 0 0 0 1	0.210 0.033 0.082
ADENOMA	(3512	) IN 105-106	2	22 15 18 24 20	
Spontaneous tumor pct: <= 1% in ctrl. - Total				0 0 0 0 1	
KIDNEY	(37	) IN 79-91	1	0 0 0 1 0	0.340 0.414 0.592
TUBULARCELLADENOMA	(3726	) IN 79-91	2	10 11 8 6 8	
Spontaneous tumor pct: <= 1% in ctrl. - Total				0 0 0 1 0	
LIVER	(40	) IN 53-78	1	1 0 0 0 0	0.598 0.601 0.628
HEPATOCELLULARADENOMA	(4002	) IN 53-78	2	5 9 9 4 4	
		IN 79-91	1	0 1 0 0 1	
		IN 79-91	2	9 10 7 7 6	

			IN 92-104	1	1	0	1	1	1	
			IN 92-104	2	9	10	8	9	11	
			IN 105-106	1	6	6	6	7	5	
			IN 105-106	2	16	9	12	17	16	
			FA 75	1	0	0	0	1	0	
			FA 75	2	44	39	37	43	43	
			FA 82	1	0	0	0	0	1	
			FA 82	2	41	34	37	42	40	
			FA 84	1	1	0	0	0	0	
			FA 84	2	38	34	35	40	39	
			FA 87	1	0	0	1	0	0	
			FA 87	2	36	31	34	40	38	
			FA 93	1	0	0	0	0	1	
			FA 93	2	32	25	27	35	32	
			FA 95	1	0	1	1	0	0	
			FA 95	2	31	23	26	31	30	
			FA 96	1	0	0	1	0	0	
			FA 96	2	31	21	24	29	28	
			FA 103	1	0	0	0	1	0	
			FA 103	2	26	16	21	24	25	
Spontaneous tumor pct: 17% in ctrl. - Total					-	9	8	10	10	9
LIVER	(40	)	IN 92-104	1	0	0	0	0	1	0.341 0.350 0.388
HEPATOCELLULARCARCINOMA	(4003	)	IN 92-104	2	10	10	10	10	10	
			IN 105-106	1	0	0	5	0	1	
			IN 105-106	2	22	15	13	24	20	
			FA 77	1	1	0	0	0	0	
			FA 77	2	43	39	37	43	43	
			FA 83	1	0	0	0	0	1	
			FA 83	2	39	34	35	40	39	
			FA 84	1	0	1	0	0	0	
			FA 84	2	39	33	35	40	39	
			FA 90	1	0	0	1	0	0	
			FA 90	2	32	28	31	37	37	
			FA 91	1	0	1	1	1	0	
			FA 91	2	32	26	30	36	36	
			FA 93	1	0	0	0	0	2	
			FA 93	2	32	25	27	35	31	
			FA 95	1	0	1	1	0	0	
			FA 95	2	31	23	26	31	30	
			FA 96	1	0	0	0	1	0	
			FA 96	2	31	21	25	28	28	
Spontaneous tumor pct: 4% in ctrl. - Total					-	1	3	8	2	5
LIVER	(40	)	IN 92-104	1	0	1	0	0	0	0.797 0.795 0.835
HEMANGIOMA	(4025	)	IN 92-104	2	10	10	11	11	13	
			IN 105-106	1	1	2	2	2	1	
			IN 105-106	2	21	13	16	22	20	
Spontaneous tumor pct: 4% in ctrl. - Total					-	1	3	2	2	1
LIVER	(40	)	IN 92-104	1	0	0	0	0	1	0.380 0.383 0.437
HEMANGIOSARCOMA	(4026	)	IN 92-104	2	10	10	9	11	12	
			IN 105-106	1	0	0	0	1	0	
			IN 105-106	2	22	15	18	23	21	
			FA 65	1	0	0	0	1	0	
			FA 65	2	46	45	44	46	44	
			FA 69	1	0	0	0	0	1	

FA 69	2	46 43 41 44 43	
FA 87	1	0 0 0 1 0	
FA 87	2	36 31 35 39 38	
FA 88	1	0 0 1 0 0	
FA 88	2	35 31 33 37 37	
FA 91	1	0 0 1 0 0	
FA 91	2	32 27 30 37 36	
FA 98	1	0 0 1 0 0	
FA 98	2	30 20 23 27 26	
FA 99	1	0 1 0 0 0	
FA 99	2	29 18 23 27 26	
FA 100	1	0 0 1 0 0	
FA 100	2	27 17 21 27 26	
Spontaneous tumor pct: <= 1% in ctrl. - Total		-	0 1 4 3 2
LIVER	(40 )	IN 105-106 1	0 0 0 1 0
CHOLANGIOMA	(4031 )	IN 105-106 2	22 15 18 23 21
	FA 61	1	0 0 0 0 1
	FA 61	2	46 45 45 47 44
Spontaneous tumor pct: <= 1% in ctrl. - Total		-	0 0 0 1 1
LIVER	(40 )	FA 95 1	0 0 0 0 1
ANAPLASTICCARCINOMA	(4037 )	FA 95 2	31 24 27 31 29
Spontaneous tumor pct: <= 1% in ctrl. - Total		-	0 0 0 0 1
LUNG	(41 )	IN 53-78 1	0 0 0 1 0
ALVEOLAR/BRONCHIOLARADEN	(4101 )	IN 53-78 2	6 9 9 4 3
		IN 79-91 1	0 2 1 2 0
		IN 79-91 2	10 9 7 5 8
		IN 92-104 1	1 2 2 2 3
		IN 92-104 2	8 9 9 9 9
		IN 105-106 1	3 5 5 9 7
		IN 105-106 2	19 10 13 15 14
	FA 61	1	0 0 0 0 1
	FA 61	2	46 45 45 47 43
	FA 98	1	1 0 0 0 0
	FA 98	2	29 20 24 27 26
Spontaneous tumor pct: 14% in ctrl. - Total		-	5 9 8 14 11
LUNG	(41 )	IN 79-91 1	0 0 0 1 1
ALVEOLAR/LRONCHIOLARCARC	(4102 )	IN 79-91 2	8 10 7 5 7
		IN 92-104 1	0 0 0 0 1
		IN 92-104 2	9 11 7 10 11
		IN 105-106 1	5 0 2 2 5
		IN 105-106 2	17 15 16 22 16
	FA 82	1	1 0 1 1 0
	FA 82	2	40 34 36 41 40
	FA 86	1	1 0 0 0 0
	FA 86	2	36 31 35 40 38
	FA 88	1	0 1 0 0 0
	FA 88	2	35 30 34 37 36
	FA 92	1	0 0 1 0 0
	FA 92	2	32 26 28 35 33
	FA 96	1	0 0 0 1 0
	FA 96	2	31 21 25 28 28
	FA 99	1	1 0 1 0 0
	FA 99	2	28 19 22 27 26

			FA 100	1	0	0	1	0	0	
			FA 100	2	27	17	21	27	26	
			FA 104	1	0	0	1	0	0	
			FA 104	2	24	16	18	24	24	
Spontaneous tumor pct: 9%		in ctrl. - Total	-	-	8	1	7	5	7	
LYMPHNODE	(42	)	IN 105-106	1	0	0	1	2	0	0.834 0.830 0.859
LYMPHOSARCOMA	(4202	)	IN 105-106	2	22	14	17	22	21	
			FA 27	1	1	0	0	0	0	
			FA 27	2	49	48	50	50	50	
			FA 68	1	0	1	0	0	0	
			FA 68	2	46	44	41	44	44	
			FA 72	1	0	1	0	0	0	
			FA 72	2	46	40	40	44	43	
			FA 74	1	0	0	1	0	0	
			FA 74	2	45	39	38	44	43	
			FA 88	1	0	1	0	0	0	
			FA 88	2	35	30	34	37	37	
			FA 92	1	0	0	1	0	0	
			FA 92	2	32	26	28	35	34	
			FA 93	1	0	0	0	0	1	
			FA 93	2	32	25	27	35	32	
			FA 94	1	0	0	0	1	0	
			FA 94	2	32	25	27	32	31	
			FA 101	1	0	0	0	1	0	
			FA 101	2	27	17	21	26	26	
			FA 105	1	0	1	0	0	0	
			FA 105	2	22	14	18	24	21	
Spontaneous tumor pct: 5%		in ctrl. - Total	-	-	1	4	3	4	1	
LYMPHNODE	(42	)	IN 105-106	1	0	1	0	0	0	1.000 0.791 0.894
MYELOIDLEUKEMIA	(4203	)	IN 105-106	2	22	14	18	24	21	
Spontaneous tumor pct: <= 1%		in ctrl. - Total	-	-	0	1	0	0	0	
LYMPHNODE	(42	)	IN 105-106	1	1	0	1	0	0	0.741 0.742 0.796
HISTIOCYTICSARCOMA	(4204	)	IN 105-106	2	21	15	17	24	21	
			FA 44	1	0	0	1	0	0	
			FA 44	2	48	48	46	50	48	
			FA 74	1	1	0	0	0	0	
			FA 74	2	44	39	39	44	43	
			FA 87	1	0	0	0	0	1	
			FA 87	2	36	31	35	40	37	
			FA 99	1	1	0	0	0	0	
			FA 99	2	28	19	23	27	26	
Spontaneous tumor pct: 3%		in ctrl. - Total	-	-	3	0	2	0	1	
LYMPHNODE	(42	)	IN 105-106	1	0	0	0	0	1	0.210 0.033 0.082
METASTASIS,CARCINOMAOF	(4217	)	IN 105-106	2	22	15	18	24	20	
Spontaneous tumor pct: <= 1%		in ctrl. - Total	-	-	0	0	0	0	1	
PITUITARY	(54	)	FA 91	1	0	0	1	0	0	0.638 0.712 0.839
CARCINOMA	(5403	)	FA 91	2	32	27	30	37	36	
Spontaneous tumor pct: <= 1%		in ctrl. - Total	-	-	0	0	1	0	0	
PROSTATE	(56	)	FA 93	1	0	0	0	0	1	0.217 0.036 0.087
ADENOMA	(5608	)	FA 93	2	32	25	27	35	32	
Spontaneous tumor pct: <= 1%		in ctrl. - Total	-	-	0	0	0	0	1	

SALIVARYGLAND	(58	) IN 79-91	1	0	0	1	0	0	0.522	0.660	0.805
HEMANGIOMA	(5802	) IN 79-91	2	10	11	7	7	8			
Spontaneous tumor pct: <= 1% in ctrl. - Total			-	0	0	1	0	0			
SKINMISCELLANEOUS	(61	) FA 96	1	0	0	0	1	0	0.425	0.464	0.636
SQUAMOUSCELLCARCINOMA	(6109	) FA 96	2	31	21	25	28	28			
Spontaneous tumor pct: <= 1% in ctrl. - Total			-	0	0	0	1	0			
SKINMISCELLANEOUS	(61	) IN 92-104	1	1	0	0	0	0	1.000	0.789	0.890
SQUAMOUSCELLPAPILLOMA	(6112	) IN 92-104	2	9	11	11	11	13			
Spontaneous tumor pct: <= 1% in ctrl. - Total			-	1	0	0	0	0			
SPLEEN	(63	) IN 105-106	1	0	2	0	0	0	0.828	0.813	0.873
HEMANGIOSARCOMA	(6313	) IN 105-106	2	22	13	18	24	21			
		FA 95	1	0	0	0	1	0			
		FA 95	2	31	24	27	30	30			
Spontaneous tumor pct: 2% in ctrl. - Total			-	0	2	0	1	0			
SPLEEN	(63	) IN 105-106	1	0	0	2	1	0	0.785	0.820	0.872
HEMANGIOMA	(6316	) IN 105-106	2	22	15	16	23	21			
		FA 99	1	0	1	0	0	0			
		FA 99	2	29	18	23	27	26			
Spontaneous tumor pct: <= 1% in ctrl. - Total			-	0	1	2	1	0			
STOMACH	(64	) FA 103	1	0	0	1	0	0	0.628	0.709	0.837
SQUAMOUSCELLCARCINOMA	(6416	) FA 103	2	26	16	20	25	25			
Spontaneous tumor pct: <= 1% in ctrl. - Total			-	0	0	1	0	0			
SUBCUTANEOUSTISSUE	(65	) IN 92-104	1	0	0	0	1	0	0.428	0.483	0.648
HEMANGIOSARCOMA	(6508	) IN 92-104	2	10	11	11	10	13			
Spontaneous tumor pct: <= 1% in ctrl. - Total			-	0	0	0	1	0			
SUBCUTANEOUSTISSUE	(65	) IN 105-106	1	0	0	1	0	0	0.630	0.708	0.838
FIBROSARCOMA	(6511	) IN 105-106	2	22	15	17	24	21			
Spontaneous tumor pct: <= 1% in ctrl. - Total			-	0	0	1	0	0			
TESTIS	(66	) IN 79-91	1	0	1	0	0	0	0.499	0.420	0.521
INTERSTITIALCELLADENOMA	(6611	) IN 79-91	2	10	10	8	7	8			
		IN 105-106	1	0	1	0	0	1			
		IN 105-106	2	22	14	18	24	20			
Spontaneous tumor pct: 2% in ctrl. - Total			-	0	2	0	0	1			
TESTIS	(66	) IN 105-106	1	0	0	1	0	0	0.630	0.708	0.838
PAPILLARYCYSTADENOMA,RE	(6616	) IN 105-106	2	22	15	17	24	21			
Spontaneous tumor pct: <= 1% in ctrl. - Total			-	0	0	1	0	0			
THYROID	(68	) IN 92-104	1	0	0	0	2	0	0.449	0.476	0.596
FOLLICULARCELLADENOMA	(6807	) IN 92-104	2	10	11	11	9	13			
Spontaneous tumor pct: <= 1% in ctrl. - Total			-	0	0	0	2	0			
THYROID	(68	) IN 105-106	1	0	0	0	1	0	0.450	0.473	0.645
FOLLICULARCELLCARCINOMA	(6809	) IN 105-106	2	22	15	18	23	21			
Spontaneous tumor pct: <= 1% in ctrl. - Total			-	0	0	0	1	0			
TONGUE	(69	) IN 105-106	1	0	0	0	1	0	0.450	0.473	0.645
SQUAMOUSPAPILLOMA	(6904	) IN 105-106	2	22	15	18	23	21			



Spontaneous tumor pct: <= 1% in ctrl. - Total	-	0	0	0	1	0	
TAIL	(85 ) IN 105-106 1	0	0	0	0	1	0.210 0.033 0.082
FIBROMA	(8502 ) IN 105-106 2	22	15	18	24	20	
Spontaneous tumor pct: <= 1% in ctrl. - Total	-	0	0	0	0	1	

**APPEARS THIS WAY  
ON ORIGINAL**

Table 5b

Analysis of Carcinogenic Potential in Female Mouse  
Test of Dose-Response (Tumor) Positive Linear Trend  
Study No. A1B2C37X8YZ9

Run Date & Time: March 13, 2000 (14:12)

Source: c:\ng\XAnimalX.txt

Note: Dose Levels Included: CTRL1 CTRL2 LOW MED HIGH (0 0 0.3 1 3)  
Missing value in Tumor-Caused Death is treated as tumor not causing death  
Tumor Type: IN: Incidental (nonfatal) tumor, FA: Fatal tumor.

ORGAN/TISSUE NAME AND TUMOR NAME	(ORG#) (TMR#)	TUMOR TIME TYPES STRATA	ROW NO.	2x2 CONTINGENCY -----TABLES-----	EXACT ASYMP ASYMP PROB PROB PROB. /CONT CORR =P(STAT .GE. OBSERVED)
ADRENAL	(1	) IN 92-104	1	1 0 0 0 0	1.000 0.795 0.895
PHEOCHROMOCYTOMA	(110	) IN 92-104	2	4 8 9 8 9	
Spontaneous tumor pct: <= 1% in ctrl. - Total			-	1 0 0 0 0	
ADRENAL	(1	) FA 86	1	0 0 1 0 0	0.660 0.709 0.839
PHEOCHROMOCYTOMA	(111	) FA 86	2	27 29 36 37 35	
Spontaneous tumor pct: <= 1% in ctrl. - Total			-	0 0 1 0 0	
ADRENAL	(1	) IN 105-106	1	0 0 0 1 0	0.435 0.465 0.642
CORTICALCARCINOMA	(118	) IN 105-106	2	16 17 24 23 20	
Spontaneous tumor pct: <= 1% in ctrl. - Total			-	0 0 0 1 0	
BRAIN	(10	) FA 76	1	0 0 0 0 1	0.213 0.034 0.083
GLIOMA	(1003	) FA 76	2	32 37 39 39 39	
Spontaneous tumor pct: <= 1% in ctrl. - Total			-	0 0 0 0 1	
HARDERIANGLAND	(28	) IN 53-78	1	0 0 2 0 0	0.078 0.058 0.082
ADENOMA	(2803	) IN 53-78	2	17 13 5 7 12	
		IN 79-91	1	1 0 0 0 0	
		IN 79-91	2	8 10 7 7 7	
		IN 92-104	1	0 0 0 0 2	
		IN 92-104	2	5 8 9 8 7	
		IN 105-106	1	0 0 0 0 1	
		IN 105-106	2	16 17 24 24 19	
Spontaneous tumor pct: <= 1% in ctrl. - Total			-	1 0 2 0 3	
HARDERIANGLAND	(28	) FA 91	1	0 0 1 0 0	0.671 0.709 0.840
ADENOCARCINOMA	(2805	) FA 91	2	21 26 33 32 30	
Spontaneous tumor pct: <= 1% in ctrl. - Total			-	0 0 1 0 0	
LIVER	(40	) IN 53-78	1	1 0 0 0 0	0.357 0.370 0.432
HEPATOCELLULARADENOMA	(4001	) IN 53-78	2	16 13 7 7 12	
		IN 79-91	1	1 0 0 0 0	
		IN 79-91	2	8 10 7 7 7	
		IN 105-106	1	2 0 0 2 2	
		IN 105-106	2	14 17 24 22 18	
Spontaneous tumor pct: 4% in ctrl. - Total			-	4 0 0 2 2	
LIVER	(40	) IN 105-106	1	0 0 2 0 1	0.509 0.508 0.597
HEPATOCELLULARCARCINOMA	(4002	) IN 105-106	2	16 17 22 24 19	
		FA 89	1	1 0 0 0 0	

		FA 89	2	23	28	34	35	33	
Spontaneous tumor pct: <= 1% in ctrl.		- Total	-	1	0	2	0	1	
LIVER	(40	) IN 92-104	1	0	0	1	0	1	0.255 0.201 0.297
HEMANGIOMA	(4003	) IN 92-104	2	5	8	8	8	8	
Spontaneous tumor pct: <= 1% in ctrl.		- Total	-	0	0	1	0	1	
LIVER	(40	) FA 83	1	1	0	0	0	0	0.960 0.894 0.933
HEMANGIOSARCOMA	(4004	) FA 83	2	27	31	39	38	35	
		FA 85	1	0	1	0	0	0	
		FA 85	2	27	29	38	37	35	
		FA 86	1	0	0	1	0	0	
		FA 86	2	27	29	36	37	35	
Spontaneous tumor pct: 2% in ctrl.		- Total	-	1	1	1	0	0	
LIVER	(40	) FA 71	1	0	0	0	0	1	0.206 0.031 0.077
CHOLANGIOMA	(4024	) FA 71	2	38	42	44	41	42	
Spontaneous tumor pct: <= 1% in ctrl.		- Total	-	0	0	0	0	1	
LUNG	(41	) IN 53-78	1	3	3	0	0	1	0.807 0.805 0.828
ALVEOLAR/BRONCHIOLARADEN	(4108	) IN 53-78	2	14	10	7	7	11	
		IN 79-91	1	1	0	0	1	1	
		IN 79-91	2	8	10	7	5	6	
		IN 92-104	1	1	1	2	1	3	
		IN 92-104	2	4	7	7	7	6	
		IN 105-106	1	1	3	6	1	0	
		IN 105-106	2	15	14	18	23	20	
		FA 90	1	0	0	0	1	0	
		FA 90	2	22	27	34	32	32	
Spontaneous tumor pct: 13% in ctrl.		- Total	-	6	7	8	4	5	
LUNG	(41	) IN 53-78	1	0	0	1	0	0	0.411 0.413 0.467
ALVEOLAR/BRONCHIOLARCARC	(4109	) IN 53-78	2	17	13	6	7	12	
		IN 79-91	1	0	1	0	0	0	
		IN 79-91	2	8	9	7	7	7	
		IN 92-104	1	0	0	0	0	1	
		IN 92-104	2	5	8	9	8	8	
		IN 105-106	1	0	3	1	0	2	
		IN 105-106	2	16	14	23	23	18	
		FA 87	1	1	0	0	0	0	
		FA 87	2	26	29	35	37	35	
		FA 105	1	0	0	0	1	0	
		FA 105	2	16	17	24	23	20	
Spontaneous tumor pct: 5% in ctrl.		- Total	-	1	4	2	1	3	
LYMPHNODE	(42	) IN 105-106	1	1	2	3	4	3	0.762 0.765 0.788
LYMPHOSARCOMA	(4201	) IN 105-106	2	15	15	21	20	17	
		FA 10	1	1	0	0	0	0	
		FA 10	2	49	50	50	50	50	
		FA 38	1	0	1	0	0	0	
		FA 38	2	48	49	49	48	50	
		FA 42	1	0	0	0	1	0	
		FA 42	2	47	49	48	47	50	
		FA 66	1	1	0	0	0	0	
		FA 66	2	41	45	44	45	44	
		FA 72	1	0	1	0	0	0	
		FA 72	2	37	41	44	41	41	

FA 73	1	0	1	0	0	0	
FA 73	2	35	40	42	41	41	
FA 78	1	0	1	0	0	0	
FA 78	2	31	35	40	39	37	
FA 80	1	0	1	0	0	0	
FA 80	2	30	32	39	38	36	
FA 81	1	0	1	0	0	0	
FA 81	2	29	31	39	38	36	
FA 83	1	0	0	0	1	0	
FA 83	2	28	31	39	37	35	
FA 84	1	0	0	1	0	0	
FA 84	2	27	30	38	37	35	
FA 86	1	0	0	1	0	0	
FA 86	2	27	29	36	37	35	
FA 87	1	0	0	0	1	0	
FA 87	2	27	29	35	36	35	
FA 94	1	0	0	1	1	0	
FA 94	2	21	23	31	30	28	
FA 96	1	0	0	0	1	0	
FA 96	2	20	23	29	28	28	
FA 98	1	0	0	0	0	1	
FA 98	2	19	22	28	27	25	
FA 99	1	0	0	1	0	1	
FA 99	2	18	22	27	26	24	
FA 102	1	1	0	0	0	0	
FA 102	2	16	20	27	24	23	
FA 103	1	0	1	0	0	0	
FA 103	2	16	18	26	24	23	
Spontaneous tumor pct: 13% in ctrl. - Total		-	4	9	7	9	5
LYMPHNODE	(42	) FA 85	1	0	0	1	0 0
MYELOIDLEUKEMIA	(4202	) FA 85	2	27	30	37	0.658 0.707 0.838
Spontaneous tumor pct: <= 1% in ctrl. - Total		-	0	0	1	0 0	
LYMPHNODE	(42	) IN 105-106	1	0	0	0	0.730 0.734 0.773
HISTIOCYTICSARCOMA	(4203	) IN 105-106	2	16	17	24	
FA 60	1		0	0	1	0 0	
FA 60	2		45	46	46	46 48	
FA 63	1		0	0	1	0 0	
FA 63	2		44	45	44	46 47	
FA 65	1		1	0	0	0 0	
FA 65	2		42	45	44	46 46	
FA 70	1		0	0	0	0 1	
FA 70	2		38	42	44	41 43	
FA 75	1		0	1	0	1 0	
FA 75	2		32	39	40	39 40	
FA 92	1		0	0	0	1 0	
FA 92	2		21	25	33	31 29	
FA 95	1		0	0	0	1 0	
FA 95	2		20	23	29	29 28	
FA 97	1		0	0	1	0 0	
FA 97	2		19	23	28	27 27	
FA 98	1		0	0	0	1 0	
FA 98	2		19	22	28	26 26	
FA 100	1		1	0	0	0 0	
FA 100	2		17	22	27	25 23	
FA 104	1		0	0	1	0 0	

		FA 104	2	16	17	24	24	21	
Spontaneous tumor pct: 3%		in ctrl. - Total	-	2	1	4	5	1	
MAMMARYGLAND	(45	) IN 105-106	1	1	0	1	0	0	0.688 0.676 0.744
ADENOCARCINOMA	(4501	) IN 105-106	2	15	17	23	24	20	
		FA 66	1	1	0	0	0	0	
		FA 66	2	41	45	44	45	44	
		FA 71	1	0	0	0	0	1	
		FA 71	2	38	42	44	41	42	
		FA 77	1	0	1	0	0	0	
		FA 77	2	32	36	40	39	39	
Spontaneous tumor pct: 3%		in ctrl. - Total	-	2	1	1	0	1	
MAMMARYGLAND	(45	) IN 105-106	1	0	0	1	0	0	0.673 0.707 0.840
ADENOMA	(4504	) IN 105-106	2	16	17	23	24	20	
Spontaneous tumor pct: <= 1%		in ctrl. - Total	-	0	0	1	0	0	
MUSCLESKELETAL	(47	) FA 73	1	1	0	0	0	0	1.000 0.780 0.887
HEMANGIOSARCOMA	(4702	) FA 73	2	34	41	42	39	41	
Spontaneous tumor pct: <= 1%		in ctrl. - Total	-	1	0	0	0	0	
OVARY	(50	) IN 105-106	1	0	1	0	0	0	1.000 0.870 0.925
ADENOCARCINOMA	(5004	) IN 105-106	2	16	16	24	24	20	
		FA 74	1	1	0	0	0	0	
		FA 74	2	32	40	42	40	40	
Spontaneous tumor pct: 2%		in ctrl. - Total	-	1	1	0	0	0	
OVARY	(50	) IN 105-106	1	0	1	1	1	0	0.748 0.771 0.842
ADENOMA	(5021	) IN 105-106	2	16	16	23	23	20	
Spontaneous tumor pct: <= 1%		in ctrl. - Total	-	0	1	1	1	0	
OVARY	(50	) IN 105-106	1	0	0	1	0	0	0.673 0.707 0.840
MESOVARIANLEIOMYOMA	(5023	) IN 105-106	2	16	17	23	24	20	
Spontaneous tumor pct: <= 1%		in ctrl. - Total	-	0	0	1	0	0	
OVARY	(50	) IN 105-106	1	0	0	0	0	1	0.198 0.029 0.074
BENIGNLUTEOMA	(5025	) IN 105-106	2	16	17	24	24	19	
Spontaneous tumor pct: <= 1%		in ctrl. - Total	-	0	0	0	0	1	
PITUITARY	(54	) IN 92-104	1	0	0	0	1	0	0.547 0.539 0.618
ADENOMA, PARSDISTALIS	(5406	) IN 92-104	2	5	8	8	7	8	
		IN 105-106	1	1	1	1	0	1	
		IN 105-106	2	15	16	23	24	19	
Spontaneous tumor pct: 2%		in ctrl. - Total	-	1	1	1	1	1	
PITUITARY	(54	) IN 105-106	1	1	0	0	1	0	0.684 0.697 0.799
ADENOMA, PARSINTERMEDIA	(5407	) IN 105-106	2	15	17	24	23	20	
Spontaneous tumor pct: <= 1%		in ctrl. - Total	-	1	0	0	1	0	
SKINMISCELLANEOUS	(61	) FA 83	1	0	1	0	0	0	1.000 0.789 0.894
BASALCELLCARCINOMA	(6106	) FA 83	2	28	30	39	38	35	
Spontaneous tumor pct: <= 1%		in ctrl. - Total	-	0	1	0	0	0	
SKINMISCELLANEOUS	(61	) IN 79-91	1	0	1	0	0	0	1.000 0.754 0.873
BENIGNKERATOACANTHOMA	(6108	) IN 79-91	2	9	9	7	7	7	
Spontaneous tumor pct: <= 1%		in ctrl. - Total	-	0	1	0	0	0	

SKINMISCELLANEOUS	(61	)	IN 105-106	1	0	0	1	0	0	0.673	0.707	0.840
SQUAMOUSCELLPAPILLOMA	(6110	)	IN 105-106	2	16	17	23	24	20			
Spontaneous tumor pct: <= 1% in ctrl. - Total				-	0	0	1	0	0			
SPLEEN	(63	)	IN 105-106	1	0	0	1	0	1	0.584	0.562	0.648
HEMANGIOSARCOMA	(6310	)	IN 105-106	2	16	17	23	24	19			
			FA 87	1	0	1	0	0	0			
			FA 87	2	27	28	35	37	35			
			FA 102	1	0	1	0	0	0			
			FA 102	2	17	19	27	24	23			
Spontaneous tumor pct: 2% in ctrl. - Total				-	0	2	1	0	1			
SUBCUTANEOUSTISSUE	(65	)	FA 66	1	1	0	0	0	0	0.588	0.636	0.727
FIBROSARCOMA	(6502	)	FA 66	2	41	45	44	45	44			
			FA 79	1	0	0	0	1	0			
			FA 79	2	30	35	40	38	36			
			FA 89	1	0	0	0	1	0			
			FA 89	2	24	28	34	34	33			
Spontaneous tumor pct: <= 1% in ctrl. - Total				-	1	0	0	2	0			
SUBCUTANEOUSTISSUE	(65	)	IN 92-104	1	0	1	0	0	0	1.000	0.795	0.895
MYXOMA	(6506	)	IN 92-104	2	5	7	9	8	9			
Spontaneous tumor pct: <= 1% in ctrl. - Total				-	0	1	0	0	0			
SUBCUTANEOUSTISSUE	(65	)	IN 105-106	1	1	0	0	0	0	1.000	0.792	0.897
BASALCELLCARCINOMA	(6510	)	IN 105-106	2	15	17	24	24	20			
Spontaneous tumor pct: <= 1% in ctrl. - Total				-	1	0	0	0	0			
THYROID	(68	)	IN 79-91	1	1	0	0	0	0	0.338	0.194	0.293
FOLLICULARCELLADENOMA	(6804	)	IN 79-91	2	8	10	7	7	7			
			IN 105-106	1	0	0	0	0	1			
			IN 105-106	2	16	17	24	24	19			
Spontaneous tumor pct: <= 1% in ctrl. - Total				-	1	0	0	0	1			
BONEMISCELLANEOUS	(7	)	IN 105-106	1	0	0	1	0	0	0.673	0.707	0.840
OSTEOMA	(703	)	IN 105-106	2	16	17	23	24	20			
Spontaneous tumor pct: <= 1% in ctrl. - Total				-	0	0	1	0	0			
UTERUS	(73	)	IN 105-106	1	0	0	1	3	1	0.598	0.612	0.671
ENDOMETRIALSTROMALSARCO	(7302	)	IN 105-106	2	16	17	23	21	19			
			FA 62	1	0	1	0	0	0			
			FA 62	2	44	45	45	46	47			
			FA 77	1	1	0	0	0	0			
			FA 77	2	31	37	40	39	39			
			FA 80	1	1	0	0	0	0			
			FA 80	2	29	33	39	38	36			
Spontaneous tumor pct: 3% in ctrl. - Total				-	2	1	1	3	1			
UTERUS	(73	)	FA 72	1	1	0	0	0	0	0.373	0.228	0.332
ADENOCARCINOMA	(7307	)	FA 72	2	36	42	44	41	41			
			FA 90	1	0	0	0	0	1			
			FA 90	2	22	27	34	33	31			
Spontaneous tumor pct: <= 1% in ctrl. - Total				-	1	0	0	0	1			
UTERUS	(73	)	IN 105-106	1	0	0	0	1	0	0.783	0.815	0.868
LEIOMYOSARCOMA	(7308	)	IN 105-106	2	16	17	24	23	20			
			FA 50	1	0	1	0	0	0			

			FA 50	2	47 48 47 46 49	
			FA 94	1	0 0 1 0 0	
			FA 94	2	21 23 31 31 28	
			FA 104	1	0 0 1 0 0	
			FA 104	2	16 17 24 24 21	
Spontaneous tumor pct: <= 1% in ctrl. - Total					-	0 1 2 1 0
UTERUS	(73	)	IN 79-91	1	0 1 0 0 1	0.464 0.473 0.528
BENIGNENDOMETRIALSTROMA	(7309	)	IN 79-91	2	9 9 7 7 6	
			IN 92-104	1	0 0 0 1 0	
			IN 92-104	2	5 8 9 7 8	
			IN 105-106	1	2 0 3 2 0	
			IN 105-106	2	14 17 21 22 20	
			FA 99	1	0 0 0 0 1	
			FA 99	2	18 22 28 26 24	
Spontaneous tumor pct: 3% in ctrl. - Total					-	2 1 3 3 2
UTERUS	(73	)	IN 79-91	1	1 0 1 0 0	0.485 0.490 0.552
LEIOMYOMA	(7318	)	IN 79-91	2	8 10 6 7 7	
			IN 105-106	1	1 1 2 1 2	
			IN 105-106	2	15 16 22 23 18	
Spontaneous tumor pct: 3% in ctrl. - Total					-	2 1 3 1 2
UTERUS	(73	)	IN 79-91	1	0 0 1 0 0	0.527 0.565 0.663
HEMANGIOSARCOMA	(7321	)	IN 79-91	2	9 10 6 6 7	
			FA 87	1	0 0 0 1 0	
			FA 87	2	27 29 35 36 35	
			FA 96	1	0 0 0 1 0	
			FA 96	2	20 23 29 28 28	
Spontaneous tumor pct: <= 1% in ctrl. - Total					-	0 0 1 2 0
UTERUS	(73	)	IN 92-104	1	1 0 0 1 0	0.688 0.716 0.810
FIBROMA	(7323	)	IN 92-104	2	4 8 9 7 9	
Spontaneous tumor pct: <= 1% in ctrl. - Total					-	1 0 0 1 0
UTERUS	(73	)	IN 92-104	1	0 1 0 0 0	1.000 0.795 0.895
HEMANGIOMA	(7325	)	IN 92-104	2	5 7 9 8 9	
Spontaneous tumor pct: <= 1% in ctrl. - Total					-	0 1 0 0 0
UTERUS	(73	)	IN 105-106	1	0 0 0 0 1	0.198 0.029 0.074
ADENOMA	(7329	)	IN 105-106	2	16 17 24 24 19	
Spontaneous tumor pct: <= 1% in ctrl. - Total					-	0 0 0 0 1
VAGINA	(74	)	FA 40	1	1 0 0 0 0	1.000 0.778 0.886
LEIOMYOSARCOMA	(7401	)	FA 40	2	46 49 48 48 50	
Spontaneous tumor pct: <= 1% in ctrl. - Total					-	1 0 0 0 0
VAGINA	(74	)	FA 91	1	0 1 0 0 0	1.000 0.794 0.896
SQUAMOUSCELLCARCINOMA	(7403	)	FA 91	2	20 25 34 32 30	
Spontaneous tumor pct: <= 1% in ctrl. - Total					-	0 1 0 0 0

Table 5c

**Analysis of Carcinogenic Potential in Male Rat  
Test of Dose-Response (Tumor) Positive Linear Trend**

Study No. A1B2C37X8YZ9

Run Date & Time: March 13, 2000 (14:40)

Source: c:\ng\XAnimalX.txt

Note: Dose Levels Included: CTRL1 CTRL2 LOW MED HIGH (0 0 0.4 1.2 2.4)  
Missing value in Tumor-Caused Death is treated as tumor not causing death  
Tumor Type: IN: Incidental (nonfatal) tumor, FA: Fatal tumor.

ORGAN/TISSUE NAME AND TUMOR NAME	(ORG#) (TMR#)	TUMOR TIME TYPES STRATA	ROW NO.	2xC CONTINGENCY -----TABLES-----	EXACT ASYMP ASYMP PROB PROB PROB /CONT CORR =P(STAT. GE. OBSERVED)
ADRENAL	(1	) IN 53-78	1	2 0 0 0 0	0.754 0.725 0.807
CORTICALADENOMA	(110	) IN 53-78	2	16 10 10 12 5	
		IN 79-91	1	0 1 0 0 0	
		IN 79-91	2	17 14 19 11 5	
		IN 92-104	1	0 1 0 0 0	
		IN 92-104	2	13 14 12 12 13	
		IN 105-106	1	0 0 0 0 1	
		IN 105-106	2	11 19 15 21 34	
Spontaneous tumor pct: 3% in ctrl. - Total				2 2 0 0 1	
ADRENAL	(1	) IN 53-78	1	0 0 2 1 0	0.846 0.837 0.861
BENIGNPHEOCHROMOCYTOMA	(111	) IN 53-78	2	18 10 8 11 5	
		IN 79-91	1	4 4 4 1 1	
		IN 79-91	2	13 11 15 10 4	
		IN 92-104	1	1 3 2 1 1	
		IN 92-104	2	12 12 10 11 12	
		IN 105-106	1	5 2 0 0 5	
		IN 105-106	2	6 17 15 21 30	
Spontaneous tumor pct: 16% in ctrl. - Total				10 9 8 3 7	
ADRENAL	(1	) IN 92-104	1	3 0 1 0 0	0.802 0.789 0.830
MALIGNANTPHEOCHROMOCYTOM	(118	) IN 92-104	2	10 14 11 12 13	
		IN 105-106	1	0 1 2 1 3	
		IN 105-106	2	11 18 13 20 32	
		FA 104	1	0 1 0 0 0	
		FA 104	2	11 19 16 21 36	
Spontaneous tumor pct: 4% in ctrl. - Total				3 2 3 1 3	
BRAIN	(10	) FA 83	1	1 0 0 0 0	1.000 0.909 0.955
GLIOMA	(1005	) FA 83	2	37 45 42 44 52	
		FA 89	1	0 1 0 0 0	
		FA 89	2	28 38 31 34 50	
Spontaneous tumor pct: 2% in ctrl. - Total				1 1 0 0 0	
CAVITYABDOMINAL	(13	) FA 100	1	0 0 0 1 0	0.507 0.436 0.635
MALIGNANTSCHWANNOMA	(1304	) FA 100	2	13 27 22 25 38	
Spontaneous tumor pct: <= 1% in ctrl. - Total				0 0 0 1 0	
DUODENUM	(21	) FA 69	1	0 0 0 0 1	0.202 0.040 0.114
ADENOCARCINOMA	(2104	) FA 69	2	54 56 51 52 53	
Spontaneous tumor pct: <= 1% in ctrl. - Total				0 0 0 0 1	



HEART	(29	)	IN 79-91	1	0	0	1	0	0	0.633	0.699	0.826
MALIGNANTENDOCARDIALSCH	(2910	)	IN 79-91	2	17	15	17	11	5			
			FA 88	1	0	0	1	0	0			
			FA 88	2	29	39	34	34	50			
Spontaneous tumor pct: <= 1% in ctrl. - Total				-	0	0	2	0	0			
JEJUNUM	(35	)	IN 105-106	1	0	0	1	0	0	0.587	0.597	0.730
ADENOCARCINOMA	(3503	)	IN 105-106	2	11	19	14	21	35			
			FA 69	1	0	0	0	1	0			
			FA 69	2	54	56	51	51	54			
Spontaneous tumor pct: <= 1% in ctrl. - Total				-	0	0	1	1	0			
KIDNEY	(37	)	FA 18	1	0	0	0	0	1	0.118	0.059	0.121
NEPHROBLASTOMA	(3705	)	FA 18	2	60	60	60	60	59			
			FA 32	1	0	0	0	1	0			
			FA 32	2	60	60	60	58	59			
Spontaneous tumor pct: <= 1% in ctrl. - Total				-	0	0	0	1	1			
KIDNEY	(37	)	IN 79-91	1	0	0	1	0	0	0.522	0.551	0.804
LIPOMA	(3710	)	IN 79-91	2	17	15	18	11	5			
Spontaneous tumor pct: <= 1% in ctrl. - Total				-	0	0	1	0	0			
KIDNEY	(37	)	IN 92-104	1	1	0	0	0	0	0.872	0.866	0.930
TUBULARCELLCARCINOMA	(3712	)	IN 92-104	2	12	15	12	12	13			
			IN 105-106	1	0	0	1	0	0			
			IN 105-106	2	11	19	14	21	35			
Spontaneous tumor pct: <= 1% in ctrl. - Total				-	1	0	1	0	0			
KIDNEY	(37	)	IN 92-104	1	0	0	0	1	0	0.384	0.322	0.532
HEMANGIOSARCOMA	(3713	)	IN 92-104	2	13	15	12	11	13			
Spontaneous tumor pct: <= 1% in ctrl. - Total				-	0	0	0	1	0			
LIVER	(40	)	IN 105-106	1	0	0	0	0	1	0.346	0.106	0.225
HEPATOCELLULARADENOMA	(4006	)	IN 105-106	2	11	19	15	21	34			
Spontaneous tumor pct: <= 1% in ctrl. - Total				-	0	0	0	0	1			
LUNG	(41	)	IN 53-78	1	0	0	0	1	0	0.309	0.193	0.422
ALVEOLAR/BRONCHIOLARADEN	(4114	)	IN 53-78	2	18	10	10	11	5			
Spontaneous tumor pct: <= 1% in ctrl. - Total				-	0	0	0	1	0			
LYMPHNODE	(42	)	IN 105-106	1	0	1	1	2	0	0.974	0.966	0.976
LYMPHOSARCOMA	(4207	)	IN 105-106	2	10	17	14	19	35			
			FA 55	1	1	0	0	0	0			
			FA 55	2	57	59	55	56	58			
			FA 83	1	0	0	1	0	0			
			FA 83	2	37	45	41	44	52			
			FA 84	1	0	0	0	1	0			
			FA 84	2	35	44	39	39	52			
			FA 87	1	1	0	0	0	0			
			FA 87	2	30	40	36	35	51			
			FA 102	1	1	0	0	1	0			
			FA 102	2	10	23	18	24	38			
			FA 105	1	0	1	0	0	0			
			FA 105	2	10	18	15	21	35			
Spontaneous tumor pct: 4% in ctrl. - Total				-	3	2	2	4	0			
LYMPHNODE	(42	)	FA 84	1	1	0	0	0	0	1.000	0.824	0.926

HISTIOCYTICSARCOMA	(4208 )	FA 84	2	34	44	39	40	52	
Spontaneous tumor pct: <= 1% in ctrl. - Total			-	1	0	0	0	0	
MAMMARYGLAND	(45 )	IN 105-106	1	0	1	1	1	0	0.860 0.853 0.910
FIBROADENOMA	(4503 )	IN 105-106	2	11	18	14	20	35	
Spontaneous tumor pct: <= 1% in ctrl. - Total			-	0	1	1	1	0	
MAMMARYGLAND	(45 )	IN 105-106	1	0	1	0	0	0	1.000 0.870 0.948
ADENOCARCINOMA	(4504 )	IN 105-106	2	11	18	15	21	35	
Spontaneous tumor pct: <= 1% in ctrl. - Total			-	0	1	0	0	0	
PANCREAS	(51 )	IN 53-78	1	0	0	0	1	0	0.002 0.000 0.001
ACINARCELLADENOMA	(5106 )	IN 53-78	2	18	10	10	11	5	
		IN 79-91	1	0	0	0	1	1	
		IN 79-91	2	17	15	19	10	4	
		IN 92-104	1	0	0	0	0	1	
		IN 92-104	2	13	15	12	12	12	
		IN 105-106	1	0	0	0	0	1	
		IN 105-106	2	11	19	15	21	34	
Spontaneous tumor pct: <= 1% in ctrl. - Total			-	0	0	0	2	3	(Exact P<0.050)
PANCREAS	(51 )	IN 79-91	1	0	1	0	0	0	0.486 0.475 0.563
ISLETCELLCARCINOMA	(5107 )	IN 79-91	2	17	14	19	11	5	
		IN 92-104	1	0	0	2	0	0	
		IN 92-104	2	13	15	10	12	13	
		IN 105-106	1	0	1	0	0	2	
		IN 105-106	2	11	18	15	21	33	
Spontaneous tumor pct: 2% in ctrl. - Total			-	0	2	2	0	2	
PANCREAS	(51 )	IN 105-106	1	1	0	0	0	0	1.000 0.870 0.948
MIXEDACINAR-ISLETCELLC	(5111 )	IN 105-106	2	10	19	15	21	35	
Spontaneous tumor pct: <= 1% in ctrl. - Total			-	1	0	0	0	0	
PANCREAS	(51 )	IN 92-104	1	0	0	1	0	0	0.268 0.258 0.389
ISLETCELLADENOMA	(5113 )	IN 92-104	2	13	15	11	12	13	
		IN 105-106	1	0	0	0	0	1	
		IN 105-106	2	11	19	15	21	34	
Spontaneous tumor pct: <= 1% in ctrl. - Total			-	0	0	1	0	1	
PITUITARY	(54 )	IN 0-52	1	0	0	0	0	1	0.282 0.271 0.303
ADENOMA, PARS DISTALIS	(5402 )	IN 0-52	2	1	1	4	4	1	
		IN 53-78	1	0	1	0	0	0	
		IN 53-78	2	18	9	10	12	5	
		IN 79-91	1	3	0	0	2	1	
		IN 79-91	2	14	15	19	9	3	
		IN 92-104	1	0	4	3	2	3	
		IN 92-104	2	13	10	9	10	9	
		IN 105-106	1	2	5	2	0	5	
		IN 105-106	2	9	14	13	21	30	
		FA 90	1	0	0	0	0	1	
		FA 90	2	26	36	30	34	49	
		FA 98	1	0	0	0	0	1	
		FA 98	2	15	30	22	27	38	
		FA 101	1	0	1	0	0	0	
		FA 101	2	12	24	20	25	38	
Spontaneous tumor pct: 13% in ctrl. - Total			-	5	11	5	4	12	

PITUITARY	(54	)	IN 105-106	1	0	1	0	0	0	1.000	0.870	0.948
ADENOMA, PARS INTERMEDIA	(5408	)	IN 105-106	2	11	18	15	21	35			
Spontaneous tumor pct: <= 1% in ctrl.	-	Total	-		0	1	0	0	0			
SKIN MISCELLANEOUS	(61	)	IN 105-106	1	0	0	1	0	0	0.536	0.514	0.630
SQUAMOUS CELL CARCINOMA	(6103	)	IN 105-106	2	11	19	14	21	35			
		FA 43	1		1	0	0	0	0			
		FA 43	2		59	59	58	58	59			
		FA 87	1		0	0	0	0	1			
		FA 87	2		32	40	36	35	50			
Spontaneous tumor pct: <= 1% in ctrl.	-	Total	-		1	0	1	0	1			
SKIN MISCELLANEOUS	(61	)	IN 92-104	1	1	0	0	0	0	0.968	0.958	0.976
BENIGN KERATOACANTHOMA	(6108	)	IN 92-104	2	12	15	12	12	13			
		IN 105-106	1		0	1	2	0	0			
		IN 105-106	2		11	18	13	21	35			
Spontaneous tumor pct: 2% in ctrl.	-	Total	-		1	1	2	0	0			
SKIN MISCELLANEOUS	(61	)	IN 92-104	1	0	1	0	0	0	1.000	0.919	0.961
BASAL CELL CARCINOMA	(6109	)	IN 92-104	2	13	14	12	12	13			
		IN 105-106	1		1	0	0	0	0			
		IN 105-106	2		10	19	15	21	35			
Spontaneous tumor pct: 2% in ctrl.	-	Total	-		1	1	0	0	0			
SKIN MISCELLANEOUS	(61	)	IN 92-104	1	0	1	0	0	0	1.000	0.800	0.917
SEBACEOUS ADENOMA	(6111	)	IN 92-104	2	13	14	12	12	13			
Spontaneous tumor pct: <= 1% in ctrl.	-	Total	-		0	1	0	0	0			
SKIN MISCELLANEOUS	(61	)	IN 105-106	1	0	0	0	1	1	0.263	0.176	0.282
SQUAMOUS CELL PAPILLOMA	(6112	)	IN 105-106	2	11	19	15	20	34			
Spontaneous tumor pct: <= 1% in ctrl.	-	Total	-		0	0	0	1	1			
SUBCUTANEOUS TISSUE	(65	)	IN 53-78	1	1	0	0	0	0	0.806	0.779	0.845
FIBROSARCOMA	(6501	)	IN 53-78	2	16	10	10	12	5			
		IN 92-104	1		0	1	0	0	0			
		IN 92-104	2		12	14	12	12	13			
		FA 48	1		0	0	0	0	1			
		FA 48	2		59	59	58	57	58			
		FA 58	1		1	0	0	0	0			
		FA 58	2		57	59	53	55	58			
		FA 97	1		1	0	0	0	0			
		FA 97	2		16	32	23	28	42			
Spontaneous tumor pct: 3% in ctrl.	-	Total	-		3	1	0	0	1			
SUBCUTANEOUS TISSUE	(65	)	IN 53-78	1	1	0	0	0	0	0.578	0.547	0.705
HEMANGIOSARCOMA	(6505	)	IN 53-78	2	17	10	10	11	5			
		FA 57	1		0	0	0	1	0			
		FA 57	2		58	59	53	55	58			
Spontaneous tumor pct: <= 1% in ctrl.	-	Total	-		1	0	0	1	0			
SUBCUTANEOUS TISSUE	(65	)	IN 53-78	1	1	0	0	0	0	0.574	0.545	0.704
MALIGNANT SCHWANNOMA	(6506	)	IN 53-78	2	17	10	10	11	5			
		FA 71	1		0	0	0	1	0			
		FA 71	2		52	55	51	49	53			
Spontaneous tumor pct: <= 1% in ctrl.	-	Total	-		1	0	0	1	0			
SUBCUTANEOUS TISSUE	(65	)	IN 79-91	1	0	0	1	0	0	0.522	0.551	0.804

LIPOMA	(6508	)	IN 79-91	2	17	15	18	11	5	
Spontaneous tumor pct: <= 1% in ctrl. - Total				-	0	0	1	0	0	
SUBCUTANEOUSTISSUE	(65	)	IN 79-91	1	1	1	0	0	1	0.423 0.405 0.474
FIBROMA	(6509	)	IN 79-91	2	16	14	19	11	4	
			IN 92-104	1	1	0	0	0	0	
			IN 92-104	2	12	15	10	12	13	
			IN 105-106	1	0	0	1	1	2	
			IN 105-106	2	11	19	14	20	33	
			FA 95	1	0	0	1	0	0	
			FA 95	2	18	34	25	32	42	
			FA 103	1	0	0	1	0	0	
			FA 103	2	11	23	17	23	38	
Spontaneous tumor pct: 3% in ctrl. - Total				-	2	1	3	1	3	
SUBCUTANEOUSTISSUE	(65	)	FA 88	1	0	0	1	0	0	0.638 0.708 0.855
UNDIFFERENTIATEDSARCOMA	(6510	)	FA 88	2	29	39	34	35	50	
Spontaneous tumor pct: <= 1% in ctrl. - Total				-	0	0	1	0	0	
TESTIS	(66	)	IN 53-78	1	1	0	0	0	0	1.000 0.868 0.938
INTERSTITIALCELLADENOMA	(6605	)	IN 53-78	2	17	10	10	12	5	
			IN 92-104	1	1	0	0	0	0	
			IN 92-104	2	12	15	12	12	13	
Spontaneous tumor pct: 2% in ctrl. - Total				-	2	0	0	0	0	
TESTIS	(66	)	IN 53-78	1	0	0	0	1	0	0.309 0.193 0.422
SERTOLICELLTUMOR	(6606	)	IN 53-78	2	18	10	10	11	5	
Spontaneous tumor pct: <= 1% in ctrl. - Total				-	0	0	0	1	0	
TESTIS	(66	)	IN 105-106	1	0	0	1	0	1	0.367 0.357 0.494
MESOTHELIOMA	(6609	)	IN 105-106	2	11	19	14	21	34	
Spontaneous tumor pct: <= 1% in ctrl. - Total				-	0	0	1	0	1	
THYMUS	(67	)	IN 92-104	1	0	0	0	1	0	0.384 0.322 0.532
BENIGNTHYMOMA	(6707	)	IN 92-104	2	13	15	12	11	13	
Spontaneous tumor pct: <= 1% in ctrl. - Total				-	0	0	0	1	0	
THYROID	(68	)	IN 79-91	1	0	1	1	0	0	0.818 0.827 0.903
C-CELLCARCINOMA	(6803	)	IN 79-91	2	17	14	18	11	5	
			IN 105-106	1	0	0	1	0	0	
			IN 105-106	2	11	19	14	21	35	
Spontaneous tumor pct: <= 1% in ctrl. - Total				-	0	1	2	0	0	
THYROID	(68	)	IN 79-91	1	4	2	4	3	1	0.115 0.106 0.125
C-CELLADENOMA	(6804	)	IN 79-91	2	13	13	15	8	4	
			IN 92-104	1	1	3	2	1	1	
			IN 92-104	2	12	12	10	11	12	
			IN 105-106	1	3	2	1	1	11	
			IN 105-106	2	8	17	14	20	24	
Spontaneous tumor pct: 13% in ctrl. - Total				-	8	7	7	5	13	
THYROID	(68	)	IN 92-104	1	0	1	0	0	0	1.000 0.800 0.917
FOLLICULARCELLADENOMA	(6808	)	IN 92-104	2	13	14	12	12	13	
Spontaneous tumor pct: <= 1% in ctrl. - Total				-	0	1	0	0	0	
TONGUE	(69	)	IN 79-91	1	0	0	0	0	1	0.074 0.002 0.020
SQUAMOUSCELLCARCINOMA	(6907	)	IN 79-91	2	17	15	19	11	4	

Spontaneous tumor pct: <= 1% in ctrl. - Total	-	0	0	0	0	1	
BONEMISCELLANEOUS (7 ) IN 92-104	1	1	0	0	0	0	1.000 0.800 0.917
OSTEOMA (701 ) IN 92-104	2	12	15	12	12	13	
Spontaneous tumor pct: <= 1% in ctrl. - Total	-	1	0	0	0	0	
URINARYBLADDER (72 ) IN 105-106	1	0	1	0	0	0	1.000 0.870 0.948
TRANSITIONALCELLPAPILLO (7206 ) IN 105-106	2	11	18	15	21	35	
Spontaneous tumor pct: <= 1% in ctrl. - Total	-	0	1	0	0	0	
MESENTERY (76 ) IN 53-78	1	0	0	0	1	0	0.309 0.193 0.422
FIBROMA (7602 ) IN 53-78	2	18	10	10	11	5	
Spontaneous tumor pct: <= 1% in ctrl. - Total	-	0	0	0	1	0	
ZYMBAL'SGLAND (87 ) FA 71	1	0	1	0	0	0	0.618 0.546 0.663
CARCINOMA (8701 ) FA 71	2	52	54	51	50	53	
	FA 83	1	0	0	0	1	0
	FA 83	2	38	45	42	43	52
	FA 85	1	0	0	0	1	0
	FA 85	2	33	42	38	38	52
Spontaneous tumor pct: <= 1% in ctrl. - Total	-	0	1	0	2	0	
BONESTERNUM (9 ) IN 105-106	1	1	0	0	0	0	1.000 0.870 0.948
OSTEOSARCOMA (902 ) IN 105-106	2	10	19	15	21	35	
Spontaneous tumor pct: <= 1% in ctrl. - Total	-	1	0	0	0	0	

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ON ORIGINAL

**Table 5d**  
**Analysis of Carcinogenic Potential in Female Rat**  
**Test of Dose-Response (Tumor) Positive Linear Trend**  
Study No. A1B2C37X8YZ9

Run Date & Time: March 13, 2000 (14:31)

Source: c:\ng\XAnimalX.txt

Note: Dose Levels Included: CTRL1 CTRL2 LOW MED HIGH (0 0 0.4 1.2 2.4)  
Missing value in Tumor-Caused Death is treated as tumor not causing death  
Tumor Type: IN: Incidental (nonfatal) tumor, FA: Fatal tumor.

ORGAN/TISSUE NAME AND TUMOR NAME	(ORG#) (TMR#)	TUMOR TIME TYPES STRATA	ROW NO.	2xC CONTINGENCY -----TABLES-----	EXACT ASYMP ASYMP PROB PROB PROB /CONT CORR =P(STAT .GE. OBSERVED)
ADRENAL	(1	) IN 79-91	1	0 1 0 0 0	0.908 0.889 0.922
CORTICALADENOMA	(114	) IN 79-91	2	4 9 4 4 10	
		IN 92-104	1	3 0 1 0 0	
		IN 92-104	2	5 10 11 7 9	
		IN 105-106	1	1 0 1 0 1	
		IN 105-106	2	40 29 35 41 30	
Spontaneous tumor pct: 4%		in ctrl. - Total	-	4 1 2 0 1	
ADRENAL	(1	) IN 105-106	1	1 0 0 0 0	1.000 0.812 0.927
BENIGNPHEOCHROMOCYTOMA	(118	) IN 105-106	2	40 29 36 41 31	
Spontaneous tumor pct: <= 1%		in ctrl. - Total	-	1 0 0 0 0	
ADRENAL	(1	) IN 92-104	1	0 0 0 0 1	0.105 0.050 0.106
MALIGNANTPHEOCHROMOCYTOM	(119	) IN 92-104	2	8 10 12 7 8	
		IN 105-106	1	0 0 0 1 0	
		IN 105-106	2	41 29 36 40 31	
Spontaneous tumor pct: <= 1%		in ctrl. - Total	-	0 0 0 1 1	
BRAIN	(10	) IN 105-106	1	2 1 0 0 0	0.990 0.962 0.979
GLIOMA	(1004	) IN 105-106	2	39 28 36 41 31	
		FA 82	1	0 1 0 0 0	
		FA 82	2	53 46 52 51 49	
		FA 101	1	0 0 1 0 0	
		FA 101	2	45 32 41 43 37	
Spontaneous tumor pct: 3%		in ctrl. - Total	-	2 2 1 0 0	
HARDERIANGLAND	(28	) IN 105-106	1	0 0 1 0 2	0.043 0.028 0.057
ADENOCARCINOMA	(2804	) IN 105-106	2	41 29 35 41 29	
Spontaneous tumor pct: <= 1%		in ctrl. - Total	-	0 0 1 0 2	(Exact P<0.050)
JEJUNUM	(35	) IN 105-106	1	0 0 0 0 1	0.174 0.031 0.099
LEIOMYOSARCOMA	(3507	) IN 105-106	2	41 29 36 41 30	
Spontaneous tumor pct: <= 1%		in ctrl. - Total	-	0 0 0 0 1	
KIDNEY	(37	) FA 103	1	0 0 0 0 1	0.175 0.032 0.100
NEPHROBLASTOMA	(3706	) FA 103	2	42 31 39 43 32	
Spontaneous tumor pct: <= 1%		in ctrl. - Total	-	0 0 0 0 1	
KIDNEY	(37	) IN 105-106	1	1 1 0 0 0	1.000 0.895 0.951
TUBULARCELLADENOMA	(3716	) IN 105-106	2	40 28 36 41 31	
Spontaneous tumor pct: 2%		in ctrl. - Total	-	1 1 0 0 0	
KIDNEY	(37	) IN 105-106	1	0 1 0 0 0	1.000 0.812 0.927

LIPOMA	(3719 )	IN 105-106	2	41	28	36	41	31	
Spontaneous tumor pct: <= 1% in ctrl.	-	Total	-	0	1	0	0	0	
LIVER	(40 )	IN 92-104	1	1	0	1	0	0	0.478 0.461 0.542
HEPATOCELLULARADENOMA	(4006 )	IN 92-104	2	7	10	11	7	9	
		IN 105-106	1	2	1	0	1	2	
		IN 105-106	2	39	28	36	40	29	
Spontaneous tumor pct: 3% in ctrl.	-	Total	-	3	1	1	1	2	
LIVER	(40 )	IN 105-106	1	2	0	0	0	0	1.000 0.895 0.951
CHOLANGIOMA	(4029 )	IN 105-106	2	39	29	36	41	31	
Spontaneous tumor pct: 2% in ctrl.	-	Total	-	2	0	0	0	0	
LYMPHNODE	(42 )	IN 0-52	1	0	0	1	0	0	0.520 0.505 0.583
LYMPHOSARCOMA	(4207 )	IN 0-52	2	1	2	2	2	3	
		IN 92-104	1	1	0	0	0	0	
		IN 92-104	2	6	10	12	7	9	
		IN 105-106	1	1	0	0	1	2	
		IN 105-106	2	40	29	36	40	29	
		FA 85	1	1	0	0	0	0	
		FA 85	2	52	45	52	50	47	
		FA 100	1	1	0	0	0	0	
		FA 100	2	45	32	43	43	38	
Spontaneous tumor pct: 3% in ctrl.	-	Total	-	4	0	1	1	2	
LYMPHNODE	(42 )	FA 86	1	0	1	0	0	0	1.000 0.935 0.967
HISTIOCYTICSARCOMA	(4212 )	FA 86	2	51	42	52	50	45	
		FA 88	1	1	0	0	0	0	
		FA 88	2	49	42	49	49	43	
		FA 92	1	0	1	0	0	0	
		FA 92	2	49	38	48	48	40	
Spontaneous tumor pct: 3% in ctrl.	-	Total	-	1	2	0	0	0	
MAMMARYGLAND	(45 )	IN 53-78	1	0	0	2	0	1	0.529 0.523 0.547
FIBROADENOMA	(4502 )	IN 53-78	2	5	8	3	5	3	
		IN 79-91	1	1	0	0	0	2	
		IN 79-91	2	2	7	2	1	3	
		IN 92-104	1	3	2	4	1	2	
		IN 92-104	2	3	7	4	4	6	
		IN 105-106	1	16	16	11	15	8	
		IN 105-106	2	25	13	25	26	23	
		FA 52	1	0	0	1	0	0	
		FA 52	2	59	58	57	58	57	
		FA 67	1	0	0	0	1	1	
		FA 67	2	55	53	56	56	53	
		FA 69	1	0	1	0	0	0	
		FA 69	2	55	52	55	56	53	
		FA 70	1	1	0	0	0	0	
		FA 70	2	54	52	54	54	53	
		FA 73	1	0	0	0	0	1	
		FA 73	2	53	51	54	52	52	
		FA 74	1	0	0	0	0	1	
		FA 74	2	53	51	54	52	51	
		FA 79	1	0	0	0	1	1	
		FA 79	2	53	49	52	51	49	
		FA 85	1	0	2	0	0	1	
		FA 85	2	53	43	52	50	46	





ISLETCELLCARCINOMA	(5113	)	IN 92-104	2	8	9	12	6	8	
			IN 105-106	1	0	0	0	2	0	
			IN 105-106	2	41	29	36	39	31	
Spontaneous tumor pct: <= 1% in ctrl.			- Total	-	0	0	0	3	1	
PITUITARY	(54	)	IN 53-78	1	0	1	0	0	0	0.906 0.901 0.912
ADENOMA, PARSDISTALIS	(5403	)	IN 53-78	2	6	7	5	5	7	
			IN 79-91	1	1	4	1	1	2	
			IN 79-91	2	2	5	2	3	8	
			IN 92-104	1	4	3	5	4	2	
			IN 92-104	2	2	4	5	0	6	
			IN 105-106	1	26	14	20	19	19	
			IN 105-106	2	15	15	16	22	12	
			FA 69	1	0	0	0	1	0	
			FA 69	2	55	53	55	55	53	
			FA 74	1	0	1	0	0	0	
			FA 74	2	53	50	54	52	52	
			FA 85	1	1	0	0	0	0	
			FA 85	2	52	45	52	50	47	
			FA 87	1	0	0	1	0	0	
			FA 87	2	51	42	50	49	43	
			FA 91	1	0	1	0	0	0	
			FA 91	2	49	39	48	48	41	
			FA 93	1	0	0	0	1	0	
			FA 93	2	49	38	48	47	40	
			FA 94	1	0	1	1	0	0	
			FA 94	2	49	37	47	47	40	
			FA 96	1	1	0	0	0	0	
			FA 96	2	46	35	46	45	40	
			FA 97	1	0	0	0	0	1	
			FA 97	2	46	34	46	44	38	
			FA 99	1	0	1	0	1	0	
			FA 99	2	46	32	43	43	38	
			FA 100	1	0	0	1	0	0	
			FA 100	2	46	32	42	43	38	
			FA 101	1	1	0	0	0	0	
			FA 101	2	44	32	42	43	37	
			FA 103	1	0	0	0	1	0	
			FA 103	2	42	31	39	42	33	
			FA 104	1	0	1	0	0	0	
			FA 104	2	41	30	38	41	31	
Spontaneous tumor pct: 51% in ctrl.			- Total	-	34	27	29	28	24	
PITUITARY	(54	)	IN 79-91	1	0	0	0	1	0	0.806 0.789 0.867
CARCINOMA, PARSDISTALIS	(5406	)	IN 79-91	2	4	10	4	3	10	
			IN 105-106	1	1	1	0	0	0	
			IN 105-106	2	40	28	36	41	31	
Spontaneous tumor pct: 2% in ctrl.			- Total	-	1	1	0	1	0	
CLITORALGLAND	(55	)	IN 79-91	1	0	0	0	0	1	0.312 0.083 0.182
SQUAMOUSCELLPAPILLOMA	(5503	)	IN 79-91	2	4	10	4	4	9	
Spontaneous tumor pct: <= 1% in ctrl.			- Total	-	0	0	0	0	1	
BONEMARROW	(6	)	FA 27	1	0	1	0	0	0	1.000 0.809 0.922
MYELOIDLEUKEMIA	(603	)	FA 27	2	60	59	59	60	60	
Spontaneous tumor pct: <= 1% in ctrl.			- Total	-	0	1	0	0	0	

SKINMISCELLANEOUS	(61	) IN 105-106	1	1	0	0	0	0	1.000	0.812	0.927
BENIGNKERATOACANTHOMA	(6105	) IN 105-106	2	40	29	36	41	31			
Spontaneous tumor pct: <= 1% in ctrl. - Total				-	1	0	0	0			
SKINMISCELLANEOUS	(61	) IN 105-106	1	1	0	0	0	0	1.000	0.812	0.927
SQUAMOUSCELLCARCINOMA	(6106	) IN 105-106	2	40	29	36	41	31			
Spontaneous tumor pct: <= 1% in ctrl. - Total				-	1	0	0	0			
SKINMISCELLANEOUS	(61	) IN 105-106	1	0	0	0	1	0	0.404	0.313	0.534
SQUAMOUSCELLPAPILLOMA	(6108	) IN 105-106	2	41	29	36	40	31			
Spontaneous tumor pct: <= 1% in ctrl. - Total				-	0	0	0	1			
SPINALCORDCERVICAL	(62	) FA 87	1	0	0	1	0	0	0.605	0.663	0.837
GLIOMA	(6203	) FA 87	2	51	42	50	49	43			
Spontaneous tumor pct: <= 1% in ctrl. - Total				-	0	0	1	0			
SUBCUTANEOUSTISSUE	(65	) FA 34	1	0	1	0	0	0	1.000	0.893	0.948
HEMANGIOSARCOMA	(6502	) FA 34	2	60	58	59	60	60			
		FA 60	1	1	0	0	0	0			
		FA 60	2	57	55	56	58	57			
Spontaneous tumor pct: 2% in ctrl. - Total				-	1	1	0	0			
SUBCUTANEOUSTISSUE	(65	) IN 53-78	1	0	0	0	0	1	0.247	0.236	0.329
FIBROMA	(6504	) IN 53-78	2	6	9	5	6	6			
		IN 92-104	1	0	0	1	0	0			
		IN 92-104	2	8	10	11	6	9			
		IN 105-106	1	0	0	1	0	0			
		IN 105-106	2	41	29	35	41	31			
		FA 96	1	0	0	0	1	0			
		FA 96	2	47	35	46	44	40			
Spontaneous tumor pct: <= 1% in ctrl. - Total				-	0	0	2	1			
SUBCUTANEOUSTISSUE	(65	) IN 92-104	1	1	0	0	0	0	0.549	0.485	0.611
FIBROSARCOMA	(6505	) IN 92-104	2	7	10	12	7	9			
		FA 69	1	0	0	0	1	0			
		FA 69	2	55	53	55	55	53			
		FA 82	1	0	0	0	1	0			
		FA 82	2	53	47	52	50	49			
Spontaneous tumor pct: <= 1% in ctrl. - Total				-	1	0	0	2			
SUBCUTANEOUSTISSUE	(65	) IN 105-106	1	1	0	0	0	0	1.000	0.812	0.927
CARCINOSARCOMA	(6507	) IN 105-106	2	40	29	36	41	31			
Spontaneous tumor pct: <= 1% in ctrl. - Total				-	1	0	0	0			
THYMUS	(67	) IN 105-106	1	1	0	0	0	0	1.000	0.812	0.927
BENIGNTHYMOMA	(6708	) IN 105-106	2	40	29	36	41	31			
Spontaneous tumor pct: <= 1% in ctrl. - Total				-	1	0	0	0			
THYMUS	(67	) FA 102	1	0	0	1	0	0	0.612	0.669	0.841
MALIGNANTSCHWANNOMA	(6712	) FA 102	2	44	32	40	43	36			
Spontaneous tumor pct: <= 1% in ctrl. - Total				-	0	0	1	0			
THYMUS	(67	) IN 105-106	1	0	0	1	0	0	0.606	0.665	0.841
MALIGNANTTHYMOMA	(6713	) IN 105-106	2	41	29	35	41	31			
Spontaneous tumor pct: <= 1% in ctrl. - Total				-	0	0	1	0			
THYROID	(68	) IN 79-91	1	1	1	1	0	3	0.148	0.140	0.159

C-CELLADENOMA	(6803	)	IN 79-91	2	3	9	3	4	7	
			IN 92-104	1	1	2	1	2	2	
			IN 92-104	2	7	8	11	5	7	
			IN 105-106	1	18	8	2	3	14	
			IN 105-106	2	23	21	34	38	17	
Spontaneous tumor pct: 26%			in ctrl. - Total	-	20	11	4	5	19	
THYROID	(68	)	IN 92-104	1	1	0	0	0	0	0.924 0.903 0.943
C-CELLCARCINOMA	(6806	)	IN 92-104	2	7	10	12	7	9	
			IN 105-106	1	1	0	2	0	0	
			IN 105-106	2	40	29	34	41	31	
Spontaneous tumor pct: 2%			in ctrl. - Total	-	2	0	2	0	0	
THYROID	(68	)	IN 105-106	1	0	0	0	0	1	0.174 0.031 0.099
FOLLICULARCELLADENOMA	(6809	)	IN 105-106	2	41	29	36	41	30	
Spontaneous tumor pct: <= 1%			in ctrl. - Total	-	0	0	0	0	1	
THYROID	(68	)	IN 105-106	1	0	0	0	1	0	0.404 0.313 0.534
FOLLICULARCELLCARCINOMA	(6810	)	IN 105-106	2	41	29	36	40	31	
Spontaneous tumor pct: <= 1%			in ctrl. - Total	-	0	0	0	1	0	
URINARYBLADDER	(72	)	IN 105-106	1	0	0	0	0	1	0.175 0.032 0.100
TRANSITIONALCELLPAPILLO	(7207	)	IN 105-106	2	40	29	36	41	30	
Spontaneous tumor pct: <= 1%			in ctrl. - Total	-	0	0	0	0	1	
UTERUS	(73	)	FA 81	1	0	1	0	0	0	1.000 0.808 0.923
CARCINOSARCOMA	(7310	)	FA 81	2	53	47	52	51	49	
Spontaneous tumor pct: <= 1%			in ctrl. - Total	-	0	1	0	0	0	
UTERUS	(73	)	IN 79-91	1	0	1	0	0	1	0.546 0.365 0.500
SQUAMOUSCELLPAPILLOMA	(7311	)	IN 79-91	2	4	9	4	4	9	
Spontaneous tumor pct: <= 1%			in ctrl. - Total	-	0	1	0	0	1	
UTERUS	(73	)	IN 79-91	1	0	1	1	0	1	0.766 0.757 0.789
BENIGNENDOMETRIALSTROMA	(7313	)	IN 79-91	2	4	9	3	4	9	
			IN 92-104	1	2	0	0	1	1	
			IN 92-104	2	6	10	12	6	8	
			IN 105-106	1	11	2	1	8	2	
			IN 105-106	2	30	27	35	33	29	
Spontaneous tumor pct: 13%			in ctrl. - Total	-	13	3	2	9	4	
UTERUS	(73	)	FA 88	1	0	1	0	0	0	1.000 0.809 0.924
LEIOMYOSARCOMA	(7314	)	FA 88	2	50	41	49	49	43	
Spontaneous tumor pct: <= 1%			in ctrl. - Total	-	0	1	0	0	0	
UTERUS	(73	)	IN 105-106	1	1	1	2	0	0	0.158 0.139 0.183
MALIGNANTSCHWANNOMA	(7316	)	IN 105-106	2	40	28	34	41	31	
			FA 88	1	0	0	0	0	1	
			FA 88	2	50	42	49	49	42	
			FA 94	1	0	1	0	0	0	
			FA 94	2	49	37	48	47	40	
			FA 96	1	0	0	0	0	1	
			FA 96	2	47	35	46	45	39	
			FA 102	1	0	0	1	0	1	
			FA 102	2	44	32	40	43	35	
			FA 103	1	0	0	0	0	1	
			FA 103	2	42	31	39	43	32	

Spontaneous tumor pct: 3%    in ctrl. - Total		-	1	2	3	0	4	
UTERUS	(73)	) IN 105-106	1	1	0	1	1	0
SQUAMOUSCELLCARCINOMA	(7317)	) IN 105-106	2	40	29	35	40	31
		FA 104	1	0	0	1	0	0
		FA 104	2	41	31	37	41	31
Spontaneous tumor pct: <= 1% in ctrl. - Total		-	1	0	2	1	0	
0.730 0.734 0.819								
UTERUS	(73)	) IN 105-106	1	1	0	1	0	0
ADENOCARCINOMA	(7318)	) IN 105-106	2	40	29	35	41	31
		FA 96	1	0	1	0	0	0
		FA 96	2	47	34	46	45	40
Spontaneous tumor pct: 2%    in ctrl. - Total		-	1	1	1	0	0	
0.941 0.898 0.945								
UTERUS	(73)	) IN 105-106	1	1	0	0	0	0
ENDOMETRIALSTROMALSARCO	(7320)	) IN 105-106	2	40	29	36	41	31
Spontaneous tumor pct: <= 1% in ctrl. - Total		-	1	0	0	0	0	
1.000 0.812 0.927								
VAGINA	(74)	) IN 105-106	1	1	0	0	0	0
MALIGNANTSCHWANNOMA	(7402)	) IN 105-106	2	40	28	36	41	31
		FA 105	1	0	1	0	0	0
		FA 105	2	41	28	36	41	31
Spontaneous tumor pct: 2%    in ctrl. - Total		-	1	1	0	0	0	
1.000 0.895 0.951								
ZYMBAL'SGLAND	(85)	) FA 72	1	0	0	0	1	0
CARCINOMA	(8501)	) FA 72	2	54	52	54	52	53
Spontaneous tumor pct: <= 1% in ctrl. - Total		-	0	0	0	1	0	
0.398 0.329 0.543								

APPEARS THIS WAY  
ON ORIGINAL

Table 5e

Analysis of Carcinogenic Potential in Male Rat  
Test of Dose-Response (Tumor) Positive Linear Trend

Study No. A1B2C37X8YZ9

Run Date & Time: March 16, 2000 (8:14)

Source: c:\ng\XAnimalX.txt

Note: Dose Levels Included: CTRL1 CTRL2 HIGH (0 0 2.4)

Missing value in Tumor-Caused Death is treated as tumor not causing death

Tumor Type: IN: Incidental (nonfatal) tumor, FA: Fatal tumor.

ORGAN/TISSUE NAME AND TUMOR NAME	(ORG#) (TMR#)	TUMOR TIME TYPES STRATA	ROW NO.	2x2 CONTINGENCY -----TABLES-----	EXACT ASYMP ASYMP PROB PROB PROB /CONT CORR =P(STAT .GE. OBSERVED)
ADRENAL	(1	) IN 53-78	1	2 0 0	0.804 0.626 0.709
CORTICALADENOMA	(110	) IN 53-78	2	16 10 5	
		IN 79-91	1	0 1 0	
		IN 79-91	2	17 14 5	
		IN 92-104	1	0 1 0	
		IN 92-104	2	13 14 13	
		IN 105-105	1	0 0 1	
		IN 105-105	2	11 19 34	
Spontaneous tumor pct: 3%		in ctrl. - Total	-	2 2 1	
ADRENAL	(1	) IN 79-91	1	4 4 1	0.912 0.863 0.884
BENIGNPHEOCHROMOCYTOMA	(111	) IN 79-91	2	13 11 4	
		IN 92-104	1	1 3 1	
		IN 92-104	2	12 12 12	
		IN 105-105	1	5 2 5	
		IN 105-105	2	6 17 30	
Spontaneous tumor pct: 16%		in ctrl. - Total	-	10 9 7	
ADRENAL	(1	) IN 92-104	1	3 0 0	0.806 0.689 0.741
MALIGNANTPHEOCHROMOCYTOM	(118	) IN 92-104	2	10 14 13	
		IN 105-105	1	0 1 3	
		IN 105-105	2	11 18 32	
		FA 104	1	0 1 0	
		FA 104	2	11 19 36	
Spontaneous tumor pct: 4%		in ctrl. - Total	-	3 2 3	
BRAIN	(10	) FA 83	1	1 0 0	1.000 0.879 0.929
GLIOMA	(1005	) FA 83	2	37 45 52	
		FA 89	1	0 1 0	
		FA 89	2	28 38 50	
Spontaneous tumor pct: 2%		in ctrl. - Total	-	1 1 0	
DUODENUM	(21	) FA 69	1	0 0 1	0.329 0.076 0.162
ADENOCARCINOMA	(2104	) FA 69	2	54 56 53	
Spontaneous tumor pct: <= 1%		in ctrl. - Total	-	0 0 1	
KIDNEY	(37	) FA 18	1	0 0 1	0.333 0.078 0.165
NEPHROBLASTOMA	(3705	) FA 18	2	60 60 59	
Spontaneous tumor pct: <= 1%		in ctrl. - Total	-	0 0 1	

KIDNEY	(37	)	IN 92-104	1	1	0	0	1.000	0.752	0.870
TUBULARCELLCARCINOMA	(3712	)	IN 92-104	2	12	15	13			
Spontaneous tumor pct: <= 1% in ctrl. - Total				-	1	0	0			
LIVER	(40	)	IN 105-105	1	0	0	1	0.538	0.177	0.305
HEPATOCELLULARADENOMA	(4006	)	IN 105-105	2	11	19	34			
Spontaneous tumor pct: <= 1% in ctrl. - Total				-	0	0	1			
LYMPHNODE	(42	)	IN 105-105	1	0	1	0	1.000	0.984	0.990
LYMPHOSARCOMA	(4207	)	IN 105-105	2	10	17	35			
			FA 55	1	1	0	0			
			FA 55	2	57	59	58			
			FA 87	1	1	0	0			
			FA 87	2	30	40	51			
			FA 102	1	1	0	0			
			FA 102	2	10	23	38			
			FA 105	1	0	1	0			
			FA 105	2	10	18	35			
Spontaneous tumor pct: 4% in ctrl. - Total				-	3	2	0			
LYMPHNODE	(42	)	FA 84	1	1	0	0	1.000	0.791	0.892
HISTIOCYTICSARCOMA	(4208	)	FA 84	2	34	44	52			
Spontaneous tumor pct: <= 1% in ctrl. - Total				-	1	0	0			
MAMMARYGLAND	(45	)	IN 105-105	1	0	1	0	1.000	0.860	0.932
FIBROADENOMA	(4503	)	IN 105-105	2	11	18	35			
Spontaneous tumor pct: <= 1% in ctrl. - Total				-	0	1	0			
MAMMARYGLAND	(45	)	IN 105-105	1	0	1	0	1.000	0.860	0.932
ADENOCARCINOMA	(4504	)	IN 105-105	2	11	18	35			
Spontaneous tumor pct: <= 1% in ctrl. - Total				-	0	1	0			
PANCREAS	(51	)	IN 79-91	1	0	0	1	0.023	0.004	0.009
ACINARCELLADENOMA	(5106	)	IN 79-91	2	17	15	4			
			IN 92-104	1	0	0	1			
			IN 92-104	2	13	15	12			
			IN 105-105	1	0	0	1			
			IN 105-105	2	11	19	34			
Spontaneous tumor pct: <= 1% in ctrl. - Total				-	0	0	3	(Exact	P<0.050)	
PANCREAS	(51	)	IN 79-91	1	0	1	0	0.605	0.392	0.482
ISLETCELLCARCINOMA	(5107	)	IN 79-91	2	17	14	5			
			IN 105-105	1	0	1	2			
			IN 105-105	2	11	18	33			
Spontaneous tumor pct: 2% in ctrl. - Total				-	0	2	2			
PANCREAS	(51	)	IN 105-105	1	1	0	0	1.000	0.860	0.932
MIXEDACINAR-ISLETCELLC	(5111	)	IN 105-105	2	10	19	35			
Spontaneous tumor pct: <= 1% in ctrl. - Total				-	1	0	0			
PANCREAS	(51	)	IN 105-105	1	0	0	1	0.538	0.177	0.305
ISLETCELLADENOMA	(5113	)	IN 105-105	2	11	19	34			
Spontaneous tumor pct: <= 1% in ctrl. - Total				-	0	0	1			
PITUITARY	(54	)	IN 0-52	1	0	0	1	0.432	0.351	0.385
ADENOMA,PARSDISTALIS	(5402	)	IN 0-52	2	1	1	1			

		IN 53-78	1	0	1	0	
		IN 53-78	2	18	9	5	
		IN 79-91	1	3	0	1	
		IN 79-91	2	14	15	3	
		IN 92-104	1	0	4	3	
		IN 92-104	2	13	10	9	
		IN 105-105	1	2	5	5	
		IN 105-105	2	9	14	30	
		FA 90	1	0	0	1	
		FA 90	2	26	36	49	
		FA 98	1	0	0	1	
		FA 98	2	15	30	38	
		FA 101	1	0	1	0	
		FA 101	2	12	24	38	
Spontaneous tumor pct: 13% in ctrl. - Total				-	5	11	12
PITUITARY	(54	)	IN 105-105	1	0	1	0
ADENOMA, PARS INTERMEDIA	(5408	)	IN 105-105	2	11	18	35
Spontaneous tumor pct: <= 1% in ctrl. - Total				-	0	1	0
SKIN MISCELLANEOUS	(61	)	FA 43	1	1	0	0
SQUAMOUS CELL CARCINOMA	(6103	)	FA 43	2	59	59	59
			FA 87	1	0	0	1
			FA 87	2	32	40	50
Spontaneous tumor pct: <= 1% in ctrl. - Total				-	1	0	1
SKIN MISCELLANEOUS	(61	)	IN 92-104	1	1	0	0
BENIGN KERATOACANTHOMA	(6108	)	IN 92-104	2	12	15	13
			IN 105-105	1	0	1	0
			IN 105-105	2	11	18	35
Spontaneous tumor pct: 2% in ctrl. - Total				-	1	1	0
SKIN MISCELLANEOUS	(61	)	IN 92-104	1	0	1	0
BASAL CELL CARCINOMA	(6109	)	IN 92-104	2	13	14	13
			IN 105-105	1	1	0	0
			IN 105-105	2	10	19	35
Spontaneous tumor pct: 2% in ctrl. - Total				-	1	1	0
SKIN MISCELLANEOUS	(61	)	IN 92-104	1	0	1	0
SEBACEOUS ADENOMA	(6111	)	IN 92-104	2	13	14	13
Spontaneous tumor pct: <= 1% in ctrl. - Total				-	0	1	0
SKIN MISCELLANEOUS	(61	)	IN 105-105	1	0	0	1
SQUAMOUS CELL PAPILLOMA	(6112	)	IN 105-105	2	11	19	34
Spontaneous tumor pct: <= 1% in ctrl. - Total				-	0	0	1
SUBCUTANEOUS TISSUE	(65	)	IN 53-78	1	1	0	0
FIBROSARCOMA	(6501	)	IN 53-78	2	16	10	5
			IN 92-104	1	0	1	0
			IN 92-104	2	12	14	13
			FA 48	1	0	0	1
			FA 48	2	59	59	58
			FA 58	1	1	0	0
			FA 58	2	57	59	58
			FA 97	1	1	0	0
			FA 97	2	16	32	42
Spontaneous tumor pct: 3% in ctrl. - Total				-	3	1	1

SUBCUTANEOUSTISSUE	(65	) IN 53-78	1	1	0	0	1.000 0.663 0.842
HEMANGIOSARCOMA	(6505	) IN 53-78	2	17	10	5	
Spontaneous tumor pct: <= 1% in ctrl. - Total			-	1	0	0	
SUBCUTANEOUSTISSUE	(65	) IN 53-78	1	1	0	0	1.000 0.663 0.842
MALIGNANTSCHWANNOMA	(6506	) IN 53-78	2	17	10	5	
Spontaneous tumor pct: <= 1% in ctrl. - Total			-	1	0	0	
SUBCUTANEOUSTISSUE	(65	) IN 79-91	1	1	1	1	0.236 0.119 0.164
FIBROMA	(6509	) IN 79-91	2	16	14	4	
		IN 92-104	1	1	0	0	
		IN 92-104	2	12	15	13	
		IN 105-105	1	0	0	2	
		IN 105-105	2	11	19	33	
Spontaneous tumor pct: 3% in ctrl. - Total			-	2	1	3	
TESTIS	(66	) IN 53-78	1	1	0	0	1.000 0.787 0.875
INTERSTITIALCELLADENOMA	(6605	) IN 53-78	2	17	10	5	
		IN 92-104	1	1	0	0	
		IN 92-104	2	12	15	13	
Spontaneous tumor pct: 2% in ctrl. - Total			-	2	0	0	
TESTIS	(66	) IN 105-105	1	0	0	1	0.538 0.177 0.305
MESOTHELIOMA	(6609	) IN 105-105	2	11	19	34	
Spontaneous tumor pct: <= 1% in ctrl. - Total			-	0	0	1	
THYROID	(68	) IN 79-91	1	0	1	0	1.000 0.653 0.842
C-CELLCARCINOMA	(6803	) IN 79-91	2	17	14	5	
Spontaneous tumor pct: <= 1% in ctrl. - Total			-	0	1	0	
THYROID	(68	) IN 79-91	1	4	2	1	0.263 0.196 0.224
C-CELLADENOMA	(6804	) IN 79-91	2	13	13	4	
		IN 92-104	1	1	3	1	
		IN 92-104	2	12	12	12	
		IN 105-105	1	3	2	11	
		IN 105-105	2	8	17	24	
Spontaneous tumor pct: 13% in ctrl. - Total			-	8	7	13	
THYROID	(68	) IN 92-104	1	0	1	0	1.000 0.752 0.870
FOLLICULARCELLADENOMA	(6808	) IN 92-104	2	13	14	13	
Spontaneous tumor pct: <= 1% in ctrl. - Total			-	0	1	0	
TONGUE	(69	) IN 79-91	1	0	0	1	0.135 0.005 0.027
SQUAMOUSCELLCARCINOMA	(6907	) IN 79-91	2	17	15	4	
Spontaneous tumor pct: <= 1% in ctrl. - Total			-	0	0	1	
BONEMISCELLANEOUS	(7	) IN 92-104	1	1	0	0	1.000 0.752 0.870
OSTEOMA	(701	) IN 92-104	2	12	15	13	
Spontaneous tumor pct: <= 1% in ctrl. - Total			-	1	0	0	
URINARYBLADDER	(72	) IN 105-105	1	0	1	0	1.000 0.860 0.932
TRANSITIONALCELLPAPILLO	(7206	) IN 105-105	2	11	18	35	
Spontaneous tumor pct: <= 1% in ctrl. - Total			-	0	1	0	
ZYMBAL'SGLAND	(87	) FA 71	1	0	1	0	1.000 0.759 0.874
CARCINOMA	(8701	) FA 71	2	52	54	53	



Spontaneous tumor pct: <= 1% in ctrl. - Total	-	0	1	0	
BONESTERNUM	(9 ) IN 105-105 1	1	0	0	1.000 0.860 0.932
OSTEOSARCOMA	(902 ) IN 105-105 2	10	19	35	
Spontaneous tumor pct: <= 1% in ctrl. - Total	-	1	0	0	

APPEARS THIS WAY  
ON ORIGINAL

Table 5f  
Analysis of Carcinogenic Potential in Female Rat  
Test of Dose-Response (Tumor) Positive Linear Trend

Study No. A1B2C37X8YZ9

Run Date & Time: March 16, 2000 (8:25)

Source: c:\ng\XAnimalX.txt

Note: Dose Levels Included: CTRL1 CTRL2 HIGH (0 0 2.4)

Missing value in Tumor-Caused Death is treated as tumor not causing death

Tumor Type: IN: Incidental (nonfatal) tumor, FA: Fatal tumor.

ORGAN/TISSUE NAME AND TUMOR NAME	(ORG#) (TMR#)	TUMOR TIME TYPES STRATA	ROW NO.	2x2 CONTINGENCY -----TABLES-----	EXACT ASYMP ASYMP PROB PROB PROB /CONT CORR =P(STAT .GE. OBSERVED)
ADRENAL	(1	) IN 79-91	1	0 1 0	0.922 0.818 0.863
CORTICALADENOMA	(114	) IN 79-91	2	4 9 10	
		IN 92-104	1	3 0 0	
		IN 92-104	2	5 10 9	
		IN 105-106	1	1 0 1	
		IN 105-106	2	40 29 30	
Spontaneous tumor pct: 4%		in ctrl. - Total	-	4 1 1	
ADRENAL	(1	) IN 105-106	1	1 0 0	1.000 0.747 0.868
BENIGNPHEOCHROMOCYTOMA	(118	) IN 105-106	2	40 29 31	
Spontaneous tumor pct: <= 1%		in ctrl. - Total	-	1 0 0	
ADRENAL	(1	) IN 92-104	1	0 0 1	0.333 0.078 0.165
MALIGNANTPHEOCHROMOCYTOM	(119	) IN 92-104	2	8 10 8	
Spontaneous tumor pct: <= 1%		in ctrl. - Total	-	0 0 1	
BRAIN	(10	) IN 105-106	1	2 1 0	1.000 0.912 0.943
GLIOMA	(1004	) IN 105-106	2	39 28 31	
		FA 82	1	0 1 0	
		FA 82	2	53 46 49	
Spontaneous tumor pct: 3%		in ctrl. - Total	-	2 2 0	
HARDERIANGLAND	(28	) IN 105-106	1	0 0 2	0.092 0.016 0.034
ADENOCARCINOMA	(2804	) IN 105-106	2	41 29 29	
Spontaneous tumor pct: <= 1%		in ctrl. - Total	-	0 0 2	
JEJUNUM	(35	) IN 105-106	1	0 0 1	0.306 0.066 0.146
LEIOMYOSARCOMA	(3507	) IN 105-106	2	41 29 30	
Spontaneous tumor pct: <= 1%		in ctrl. - Total	-	0 0 1	
KIDNEY	(37	) FA 103	1	0 0 1	0.311 0.068 0.149
NEPHROBLASTOMA	(3706	) FA 103	2	42 31 32	
Spontaneous tumor pct: <= 1%		in ctrl. - Total	-	0 0 1	
KIDNEY	(37	) IN 105-106	1	1 1 0	1.000 0.827 0.897
TUBULARCELLADENOMA	(3716	) IN 105-106	2	40 28 31	
Spontaneous tumor pct: 2%		in ctrl. - Total	-	1 1 0	
KIDNEY	(37	) IN 105-106	1	0 1 0	1.000 0.747 0.868
LIPOMA	(3719	) IN 105-106	2	41 28 31	
Spontaneous tumor pct: <= 1%		in ctrl. - Total	-	0 1 0	
LIVER	(40	) IN 92-104	1	1 0 0	0.608 0.452 0.527

HEPATOCELLULARADENOMA	(4006	)	IN 92-104	2	7	10	9	
			IN 105-106	1	2	1	2	
			IN 105-106	2	39	28	29	
Spontaneous tumor pct: 3%		in ctrl.	- Total	-	3	1	2	
LIVER	(40	)	IN 105-106	1	2	0	0	1.000 0.827 0.897
CHOLANGIOMA	(4029	)	IN 105-106	2	39	29	31	
Spontaneous tumor pct: 2%		in ctrl.	- Total	-	2	0	0	
LYMPHNODE	(42	)	IN 92-104	1	1	0	0	0.622 0.471 0.544
LYMPHOSARCOMA	(4207	)	IN 92-104	2	6	10	9	
			IN 105-106	1	1	0	2	
			IN 105-106	2	40	29	29	
			FA 85	1	1	0	0	
			FA 85	2	52	45	47	
			FA 100	1	1	0	0	
			FA 100	2	45	32	38	
Spontaneous tumor pct: 3%		in ctrl.	- Total	-	4	0	2	
LYMPHNODE	(42	)	FA 86	1	0	1	0	1.000 0.881 0.925
HISTIOCYTICSARCOMA	(4212	)	FA 86	2	51	42	45	
			FA 88	1	1	0	0	
			FA 88	2	49	42	43	
			FA 92	1	0	1	0	
			FA 92	2	49	38	40	
Spontaneous tumor pct: 3%		in ctrl.	- Total	-	1	2	0	
MAMMARYGLAND	(45	)	IN 53-78	1	0	0	1	0.531 0.475 0.500
FIBROADENOMA	(4502	)	IN 53-78	2	5	8	3	
			IN 79-91	1	1	0	2	
			IN 79-91	2	2	7	3	
			IN 92-104	1	3	2	2	
			IN 92-104	2	3	7	6	
			IN 105-106	1	16	16	8	
			IN 105-106	2	25	13	23	
			FA 67	1	0	0	1	
			FA 67	2	55	53	53	
			FA 69	1	0	1	0	
			FA 69	2	55	52	53	
			FA 70	1	1	0	0	
			FA 70	2	54	52	53	
			FA 73	1	0	0	1	
			FA 73	2	53	51	52	
			FA 74	1	0	0	1	
			FA 74	2	53	51	51	
			FA 79	1	0	0	1	
			FA 79	2	53	49	49	
			FA 85	1	0	2	1	
			FA 85	2	53	43	46	
			FA 86	1	0	0	2	
			FA 86	2	51	43	43	
			FA 87	1	1	0	0	
			FA 87	2	50	42	43	
			FA 88	1	0	1	0	
			FA 88	2	50	41	43	
			FA 91	1	0	0	1	
			FA 91	2	49	40	40	

		FA 94	1	1	0	0	
		FA 94	2	48	38	40	
		FA 95	1	1	1	0	
		FA 95	2	47	35	40	
		FA 102	1	0	0	1	
		FA 102	2	44	32	35	
Spontaneous tumor pct: 39% in ctrl. - Total			-	24	23	22	
MAMMARYGLAND	(45	) IN 53-78	1	0	1	0	0.828 0.756 0.788
ADENOCARCINOMA	(4503	) IN 53-78	2	6	8	7	
		IN 92-104	1	0	3	1	
		IN 92-104	2	7	6	8	
		IN 105-106	1	7	2	4	
		IN 105-106	2	34	27	27	
		FA 102	1	1	0	0	
		FA 102	2	43	32	36	
		FA 104	1	0	1	0	
		FA 104	2	41	30	31	
Spontaneous tumor pct: 13% in ctrl. - Total			-	8	7	5	
MAMMARYGLAND	(45	) IN 92-104	1	0	1	0	1.000 0.834 0.900
ADENOMA	(4506	) IN 92-104	2	8	9	9	
		IN 105-106	1	0	1	0	
		IN 105-106	2	41	28	31	
Spontaneous tumor pct: 2% in ctrl. - Total			-	0	2	0	
OVARY	(50	) IN 105-106	1	1	0	0	1.000 0.747 0.868
BENIGNLUTEOMA	(5004	) IN 105-106	2	40	29	31	
Spontaneous tumor pct: <= 1% in ctrl. - Total			-	1	0	0	
PANCREAS	(51	) IN 105-106	1	1	0	0	1.000 0.747 0.868
ISLETCELLADENOMA	(5106	) IN 105-106	2	40	29	31	
Spontaneous tumor pct: <= 1% in ctrl. - Total			-	1	0	0	
PANCREAS	(51	) IN 92-104	1	0	0	1	0.346 0.084 0.174
ISLETCELLCARCINOMA	(5113	) IN 92-104	2	8	9	8	
Spontaneous tumor pct: <= 1% in ctrl. - Total			-	0	0	1	
PITUITARY	(54	) IN 53-78	1	0	1	0	0.921 0.894 0.905
ADENOMA,PARSDISTALIS	(5403	) IN 53-78	2	6	7	7	
		IN 79-91	1	1	4	2	
		IN 79-91	2	2	5	8	
		IN 92-104	1	4	3	2	
		IN 92-104	2	2	4	6	
		IN 105-106	1	26	14	19	
		IN 105-106	2	15	15	12	
		FA 74	1	0	1	0	
		FA 74	2	53	50	52	
		FA 85	1	1	0	0	
		FA 85	2	52	45	47	
		FA 91	1	0	1	0	
		FA 91	2	49	39	41	
		FA 94	1	0	1	0	
		FA 94	2	49	37	40	
		FA 96	1	1	0	0	
		FA 96	2	46	35	40	
		FA 97	1	0	0	1	

	FA 97	2	46 34 38	
	FA 99	1	0 1 0	
	FA 99	2	46 32 38	
	FA 101	1	1 0 0	
	FA 101	2	44 32 37	
	FA 104	1	0 1 0	
	FA 104	2	41 30 31	
Spontaneous tumor pct: 51%	in ctrl. - Total	-	34 27 24	
PITUITARY	(54 ) IN 105-106	1	1 1 0	1.000 0.827 0.897
CARCINOMA, PARSDISTALIS	(5406 ) IN 105-106	2	40 28 31	
Spontaneous tumor pct: 2%	in ctrl. - Total	-	1 1 0	
CLITORALGLAND	(55 ) IN 79-91	1	0 0 1	0.416 0.118 0.223
SQUAMOUSCELLPAPILLOMA	(5503 ) IN 79-91	2	4 10 9	
Spontaneous tumor pct: <= 1%	in ctrl. - Total	-	0 0 1	
BONEMARROW	(6 ) FA 27	1	0 1 0	1.000 0.760 0.874
MYELOIDLEUKEMIA	(603 ) FA 27	2	60 59 60	
Spontaneous tumor pct: <= 1%	in ctrl. - Total	-	0 1 0	
SKINMISCELLANEOUS	(61 ) IN 105-106	1	1 0 0	1.000 0.747 0.868
BENIGNKERATOACANTHOMA	(6105 ) IN 105-106	2	40 29 31	
Spontaneous tumor pct: <= 1%	in ctrl. - Total	-	1 0 0	
SKINMISCELLANEOUS	(61 ) IN 105-106	1	1 0 0	1.000 0.747 0.868
SQUAMOUSCELLCARCINOMA	(6106 ) IN 105-106	2	40 29 31	
Spontaneous tumor pct: <= 1%	in ctrl. - Total	-	1 0 0	
SUBCUTANEOUSTISSUE	(65 ) FA 34	1	0 1 0	1.000 0.842 0.906
HEMANGIOSARCOMA	(6502 ) FA 34	2	60 58 60	
	FA 60	1	1 0 0	
	FA 60	2	57 55 57	
Spontaneous tumor pct: 2%	in ctrl. - Total	-	1 1 0	
SUBCUTANEOUSTISSUE	(65 ) IN 53-78	1	0 0 1	0.318 0.071 0.154
FIBROMA	(6504 ) IN 53-78	2	6 9 6	
Spontaneous tumor pct: <= 1%	in ctrl. - Total	-	0 0 1	
SUBCUTANEOUSTISSUE	(65 ) IN 92-104	1	1 0 0	1.000 0.760 0.874
FIBROSARCOMA	(6505 ) IN 92-104	2	7 10 9	
Spontaneous tumor pct: <= 1%	in ctrl. - Total	-	1 0 0	
SUBCUTANEOUSTISSUE	(65 ) IN 105-106	1	1 0 0	1.000 0.747 0.868
CARCINOSARCOMA	(6507 ) IN 105-106	2	40 29 31	
Spontaneous tumor pct: <= 1%	in ctrl. - Total	-	1 0 0	
THYMUS	(67 ) IN 105-106	1	1 0 0	1.000 0.747 0.868
BENIGNTHYMOMA	(6708 ) IN 105-106	2	40 29 31	
Spontaneous tumor pct: <= 1%	in ctrl. - Total	-	1 0 0	
THYROID	(68 ) IN 79-91	1	1 1 3	0.176 0.132 0.150
C-CELLADENOMA	(6803 ) IN 79-91	2	3 9 7	
	IN 92-104	1	1 2 2	
	IN 92-104	2	7 8 7	
	IN 105-106	1	18 8 14	
	IN 105-106	2	23 21 17	

Spontaneous tumor pct: 26% in ctrl. - Total		-	20	11	19	
THYROID	(68 )	IN 92-104 1	1	0	0	1.000 0.834 0.900
C-CELLCARCINOMA	(6806 )	IN 92-104 2	7	10	9	
		IN 105-106 1	1	0	0	
		IN 105-106 2	40	29	31	
Spontaneous tumor pct: 2% in ctrl. - Total		-	2	0	0	
THYROID	(68 )	IN 105-106 1	0	0	1	0.306 0.066 0.146
FOLLICULARCELLADENOMA	(6809 )	IN 105-106 2	41	29	30	
Spontaneous tumor pct: <= 1% in ctrl. - Total		-	0	0	1	
URINARYBLADDER	(72 )	IN 105-106 1	0	0	1	0.310 0.067 0.148
TRANSITIONALCELLPAPILLO	(7207 )	IN 105-106 2	40	29	30	
Spontaneous tumor pct: <= 1% in ctrl. - Total		-	0	0	1	
UTERUS	(73 )	FA 81 1	0	1	0	1.000 0.757 0.873
CARCINOSARCOMA	(7310 )	FA 81 2	53	47	49	
Spontaneous tumor pct: <= 1% in ctrl. - Total		-	0	1	0	
UTERUS	(73 )	IN 79-91 1	0	1	1	0.670 0.403 0.524
SQUAMOUSCELLPAPILLOMA	(7311 )	IN 79-91 2	4	9	9	
Spontaneous tumor pct: <= 1% in ctrl. - Total		-	0	1	1	
UTERUS	(73 )	IN 79-91 1	0	1	1	0.939 0.893 0.911
BENIGNENDOMETRIALSTROMA	(7313 )	IN 79-91 2	4	9	9	
		IN 92-104 1	2	0	1	
		IN 92-104 2	6	10	8	
		IN 105-106 1	11	2	2	
		IN 105-106 2	30	27	29	
Spontaneous tumor pct: 13% in ctrl. - Total		-	13	3	4	
UTERUS	(73 )	FA 88 1	0	1	0	1.000 0.752 0.870
LEIOMYOSARCOMA	(7314 )	FA 88 2	50	41	43	
Spontaneous tumor pct: <= 1% in ctrl. - Total		-	0	1	0	
UTERUS	(73 )	IN 105-106 1	1	1	0	0.146 0.072 0.098
MALIGNANTSCHWANNOMA	(7316 )	IN 105-106 2	40	28	31	
		FA 88 1	0	0	1	
		FA 88 2	50	42	42	
		FA 94 1	0	1	0	
		FA 94 2	49	37	40	
		FA 96 1	0	0	1	
		FA 96 2	47	35	39	
		FA 102 1	0	0	1	
		FA 102 2	44	32	35	
		FA 103 1	0	0	1	
		FA 103 2	42	31	32	
Spontaneous tumor pct: 3% in ctrl. - Total		-	1	2	4	
UTERUS	(73 )	IN 105-106 1	1	0	0	1.000 0.747 0.868
SQUAMOUSCELLCARCINOMA	(7317 )	IN 105-106 2	40	29	31	
Spontaneous tumor pct: <= 1% in ctrl. - Total		-	1	0	0	
UTERUS	(73 )	IN 105-106 1	1	0	0	1.000 0.832 0.899
ADENOCARCINOMA	(7318 )	IN 105-106 2	40	29	31	
		FA 96 1	0	1	0	

		FA 96	2	47 34 40	
Spontaneous tumor pct: 2%	in ctrl.	- Total	-	1 1 0	
UTERUS	(73	) IN 105-106	1	1 0 0	1.000 0.747 0.868
ENDOMETRIALSTROMALSARCO	(7320	) IN 105-106	2	40 29 31	
Spontaneous tumor pct: <= 1%	in ctrl.	- Total	-	1 0 0	
VAGINA	(74	) IN 105-106	1	1 0 0	1.000 0.827 0.896
MALIGNANT SCHWANNOMA	(7402	) IN 105-106	2	40 28 31	
		FA 105	1	0 1 0	
		FA 105	2	41 28 31	
Spontaneous tumor pct: 2%	in ctrl.	- Total	-	1 1 0	

APPEARS THIS WAY  
ON ORIGINAL